10/614481 09/07/2006

Connecting via Winsock to Dialog

Logging in to Dialog

Trying 31060000009998...Open

DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ****
ENTER PASSWORD:
 ****
Welcome to DIALOG

Dialog level 05.17.01D

Last logoff: 16may07 11:47:16
Logon file405 18may07 12:37:32
*** ANNOUNCEMENTS ***
***
NEW FILES RELEASED
***BIOSIS Previews Archive (File 552)
***BIOSIS Previews 1969-2007 (File 525)
***Engineering Index Backfile (File 988)
***Trademarkscan - South Korea (File 655)

RESUMED UPDATING
***File 141, Reader's Guide Abstracts
***
RELOADS COMPLETED
***File 5, BIOSIS Previews - archival data added
***Files 340, 341 & 942, CLAIMS/U.S. Patents - 2006 reload now online
***
DATABASES REMOVED

Chemical Structure Searching now available in Prous Science Drug
Data Report (F452), Prous Science Drugs of the Future (F453),
IMS R&D Focus (F445/955), Pharmaprojects (F128/928), Beilstein
Facts (F390), Derwent Chemistry Resource (F355) and Index Chemicus
(File 302).
***
 >>>For the latest news about Dialog products, services, content<<<
 >>>and events, please visit What's New from Dialog at <<<
 >>>http://www.dialog.com/whatsnew/. You can find news about<<<
 >>>a specific database by entering HELP NEWS <file number>.<<<
>>>PROFILE is in a suspended state.
>>>Contact Dialog Customer Services to re-activate it.
* * *
SYSTEM:HOME
Cost is in DialUnits
Menu System II: D2 version 1.8.0 term=ASCII
*** DIALOG HOMEBASE(SM) Main Menu ***

 Information:
  1. Announcements (new files, reloads, etc.)
  2. Database, Rates, & Command Descriptions
  3. Help in Choosing Databases for Your Topic
  4. Customer Services (telephone assistance, training, seminars, etc.)
  5. Product Descriptions

 Connections:
  6. DIALOG(R) Document Delivery

7. Data Star(R)

/H = Help /L = Logoff /NOMENU = Command Mode

```
Enter an option number to view information or to connect to an online
 service.  Enter a BEGIN command plus a file number to search a database
(e.g., B1 for ERIC).
? b 410

       18may07 12:37:32 User217743 Session D695.1
            $0.00    0.263 DialUnits FileHomeBase
     $0.00  Estimated cost FileHomeBase
     $0.00  Estimated cost this search
     $0.00  Estimated total session cost   0.263 DialUnits

File 410:Dialog Comm.-of-Interest Newsletters 2007 /Feb
       (c) 2007 Dialog

      Set  Items  Description
      ---  -----  -----------
? set hi ;set hi
HILIGHT set on as ''
HILIGHT set on as ''
? b 155
       18may07 12:37:35 User217743 Session D695.2
            $0.00    0.115 DialUnits File410
     $0.00  Estimated cost File410
     $0.00  Estimated cost this search
     $0.00  Estimated total session cost   0.378 DialUnits

File 155:MEDLINE(R) 1950-2007/May 16
       (c) format only 2007 Dialog

      Set  Items  Description
      ---  -----  -----------
? foxa2 or fox()a2
>>>Unrecognizable Command
? s foxa2 or fox()a2
             363  FOXA2
            2828  FOX
           38359  A2
               0  FOX(W)A2
      S1     363  FOXA2 OR FOX()A2
? s (foxa2 or fox()a2)/ti
              37  FOXA2/TI
            1096  FOX/TI
           11267  A2/TI
               0  FOX/TI(W)A2/TI
      S2       37  (FOXA2 OR FOX()A2)/TI
? s s2 and py>2003
              37  S2
         2192066  PY>2003
      S3       25  S2 AND PY>2003
? s s2 not s3
              37  S2
              25  S3
      S4       12  S2 NOT S3
? t s4/3,ab/all

 4/3,AB/1
```

10/614481 09/07/2006

DIALOG(R)File 155:MEDLINE(R)
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14439796 PMID: 12911579
Functional characterization of transcription factor binding sites for HNF1-alpha, HNF3-beta (FOXA2), HNF4-alpha, Sp1 and Sp3 in the human prothrombin gene enhancer.
Ceelie H; Spaargaren-Van Riel C C; De Jong M; Bertina R M; Vos H L
Department of Haematology, Leiden University Medical Center, Leiden, the Netherlands. hceelie@lumc.nl
Journal of thrombosis and haemostasis - JTH (England) Aug 2003, 1 (8) p1688-98, ISSN 1538-7933--Print Journal Code: 101170508
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
BACKGROUND: Prothrombin is a key component in blood coagulation. Overexpression of prothrombin leads to an increased risk of venous thrombosis. Therefore, the study of the transcriptional regulation of the prothrombin gene may help to identify mechanisms of overexpression. OBJECTIVES: The aim of our study was to localize the regions within the prothrombin enhancer responsible for its activity, to identify the proteins binding to these regions, and to establish their functional importance. METHODS: We constructed a set of prothrombin promoter 5' deletion constructs containing the firefly luciferase reporter gene, which were transiently transfected in HepG2, HuH7 and HeLa cells. Putative transcription factor (TF) binding sites were evaluated by electrophoretic mobility shift assays. The functional importance of each TF binding site was evaluated by site directed mutagenesis and transient transfection of the mutant constructs. RESULTS: We confirmed the major contribution of the enhancer region to the transcriptional activity of the prothrombin promoter. Analysis of this region revealed putative binding sites for hepatocyte nuclear factor HNF4, HNF3-beta and specificity protein(Sp)1. We identified six different TFs binding to three evolutionary conserved sites in the enhancer: HNF4-alpha (site 1), HNF1-alpha, HNF3-beta and an as yet unidentified TF (site 2) and the ubiquitously expressed TFs Sp1 and Sp3 (site 3). Mutagenesis studies showed that loss of binding of HNF3-beta resulted in a considerable decrease of enhancer activity, whereas loss of HNF4-alpha or Sp1/Sp3 resulted in milder reductions. CONCLUSIONS: The prothrombin enhancer plays a major role in regulation of prothrombin expression. Six different TFs are able to bind to this region. At least three of these TFs, HNF4-alpha, HNF3-beta and Sp1/Sp3, are important in regulation of prothrombin expression.

4/3,AB/2
DIALOG(R)File 155:MEDLINE(R)
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14219289 PMID: 12642491
Joint regulation of the MAP1B promoter by HNF3beta/Foxa2 and Engrailed is the result of a highly conserved mechanism for direct interaction of homeoproteins and Fox transcription factors.
Foucher Isabelle; Montesinos Maria Luz; Volovitch Michel; Prochiantz Alain; Trembleau Alain
CNRS UMR 8542, Ecole Normale Superieure, 46 rue d'Ulm, 75230 Paris Cedex 05, France.
Development (Cambridge, England) (England) May 2003, 130 (9) p1867-76, ISSN 0950-1991--Print Journal Code: 8701744
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH

Main Citation Owner: NLM
Record type: MEDLINE; Completed

The MAP1B (Mtap1b) promoter presents two evolutionary conserved overlapping homeoproteins and Hepatocyte nuclear factor 3beta (HNF3beta/Foxa2) cognate binding sites (defining putative homeoprotein/Fox sites, HF1 and HF2). Accordingly, the promoter domain containing HF1 and HF2 is recognized by cerebellum nuclear extracts containing Engrailed and Foxa2 and has regulatory functions in primary cultures of embryonic mesmetencephalic nerve cells. Transfection experiments further demonstrate that Engrailed and Foxa2 interact physiologically in a dose-dependent manner: Foxa2 antagonizes the Engrailed-driven regulation of the MAP1B promoter, and vice versa. This led us to investigate if Engrailed and Foxa2 interact directly. Direct interaction was confirmed by pull-down experiments, and the regions participating in this interaction were identified. In Foxa2 the interacting domain is the Forkhead box DNA-binding domain. In Engrailed, two independent interacting domains exist: the homeodomain and a region that includes the Pbx-binding domain. Finally, Foxa2 not only binds Engrailed but also Lim1, Gsc and Hoxa5 homeoproteins and in the four cases Foxa2 binds at least the homeodomain. Based on the involvement of conserved domains in both classes of proteins, it is proposed that the interaction between Forkhead box transcription factors and homeoproteins is a general phenomenon.

4/3,AB/3
DIALOG(R)File 155:MEDLINE(R)

14121207 PMID: 12509444

Association between hepatocyte nuclear factor 6 (HNF-6) and FoxA2 DNA binding domains stimulates FoxA2 transcriptional activity but inhibits HNF-6 DNA binding.

Rausa Francisco M; Tan Yongjun; Costa Robert H
Department of Molecular Genetics, College of Medicine, University of Illinois at Chicago, Chicago, Illinois 60607, USA.

Molecular and cellular biology (United States) Jan 2003, 23 (2) p437-49, ISSN 0270-7306--Print Journal Code: 8109087
Contract/Grant No.: R01 GM43241; GM; NIGMS
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

In previous studies we used transgenic mice or recombinant adenovirus infection to increase hepatic expression of forkhead box A2 (FoxA2, previously called hepatocyte nuclear factor 3beta [HNF-3beta]), which caused diminished hepatocyte glycogen levels and reduced expression of glucose homeostasis genes. Because this diminished expression of FoxA2 target genes was associated with reduced levels of the Cut-Homeodomain HNF-6 transcription factor, we conducted the present study to determine whether there is a functional interaction between HNF-6 and FoxA2. Human hepatoma (HepG2) cotransfection assays demonstrated that HNF-6 synergistically stimulated FoxA2 but not FoxA1 or FoxA3 transcriptional activity, and protein-binding assays showed that this protein interaction required the HNF-6 Cut-Homeodomain and FoxA2 winged-helix DNA binding domains. Furthermore, we show that the HNF-6 Cut-Homeodomain sequences were sufficient to synergistically stimulate FoxA2 transcriptional activation by recruiting the p300/CBP coactivator proteins. This was supported by the fact that FoxA2 transcriptional synergy with HNF-6 was dependent on retention of the HNF-6 Cut domain LXXLL sequence, which mediated recruitment of the p300/CBP proteins. Moreover, cotransfection and DNA binding assays demonstrated that increased FoxA2 levels caused a decrease in HNF-6 transcriptional activation of the glucose transporter 2 (Glut-2)

promoter by interfering with the binding of HNF-6 to its target DNA sequence. These data suggest that at a FoxA-specific site, HNF-6 serves as a coactivator protein to enhance FoxA2 transcription, whereas at an HNF-6-specific site, FoxA2 represses HNF-6 transcription by inhibiting HNF-6 DNA binding activity. This is the first reported example of a liver-enriched transcription factor (HNF-6) functioning as a coactivator protein to potentiate the transcriptional activity of another liver factor, FoxA2.

4/3,AB/4
DIALOG(R)File 155:MEDLINE(R)

14031807 PMID: 12453456
A floor plate enhancer of the zebrafish netrin1 gene requires Cyclops (Nodal) signalling and the winged helix transcription factor FoxA2.
Rastegar Sepand; Albert Stephanie; Le Roux Isabelle; Fischer Nadine; Blader Patrick; Muller Ferenc; Strahle Uwe
Institut de Genetique et de Biologie Moleculaire et Cellulaire, CNRS/INSERM/ULP, B.P. 10142, 67404, Illkirch Cedex, C.U. de Strasbourg, France.
Developmental biology (United States) Dec 1 2002, 252 (1) p1-14, ISSN 0012-1606--Print Journal Code: 0372762
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The floor plate is an organising centre that controls neural differentiation and axonogenesis in the neural tube. The axon guidance molecule Netrin1 is expressed in the floor plate of zebrafish embryos. To elucidate the regulatory mechanisms underlying expression in the floor plate, we scanned the netrin1 locus for regulatory regions and identified an enhancer that drives expression in the floor plate and hypochord of transgenic embryos. The expression of the transgene is ectopically activated by Cyclops (Nodal) signals but does not respond to Hedgehog signals. The winged-helix transcription factor foxA2 (also HNF3beta, axial) is expressed in the notochord and floor plate. We show that knock-down of FoxA2 leads to loss of floor plate, while notochord and hypochord development is unaffected, suggesting a specific requirement of FoxA2 in the floor plate. The transgene is ectopically activated by FoxA2, and expression of FoxA2 leads to rescue of floor plate differentiation in mutant embryos that are deficient in Cyclops signalling. Zebrafish and mouse use different signalling systems to specify floor plate. The zebrafish netrin1 regulatory region also drives expression in the floor plate of mouse and chicken embryos. This suggests that components of the regulatory circuits controlling expression in the floor plate are conserved and that FoxA2-given its importance for midline development also in the mouse-may be one such component.

4/3,AB/5
DIALOG(R)File 155:MEDLINE(R)

13855874 PMID: 12145169
Foxa2 controls Pdx1 gene expression in pancreatic beta-cells in vivo.
Lee Catherine S; Sund Newman J; Vatamaniuk Marko Z; Matschinsky Franz M; Stoffers Doris A; Kaestner Klaus H
Department of Genetics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104-6145, USA.

Diabetes (United States) Aug 2002, 51 (8) p2546-51, ISSN 0012-1797 --Print Journal Code: 0372763
Contract/Grant No.: P30-DK-19525; DK; NIDDK; P30-DK-50306; DK; NIDDK; R01-DK-55342; DK; NIDDK
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Differentiation of early foregut endoderm into pancreatic endocrine and exocrine cells depends on a cascade of gene activation events controlled by various transcription factors. Prior in vitro analysis has suggested that the forkhead/winged helix transcription factor Foxa2 (formerly HNF-3beta) is a major upstream regulator of Pdx1, a homeobox gene essential for pancreatic development. Pdx1 is also essential for the maintenance of glucose homeostasis, as its human orthologue, IPF-1, is mutated in a subset of patients with early-onset type 2 diabetes (MODY4). To analyze the Foxa2/Pdx1 regulatory cascade during pancreatic beta-cell differentiation, we used conditional gene ablation of Foxa2 in mice. We demonstrated that the deletion of Foxa2 in beta-cell-specific knockout mice results in downregulation of Pdx1 mRNA and subsequent reduction of PDX-1 protein levels in islets. These data represent the first in vivo demonstration that Foxa2 acts upstream of Pdx1 in the differentiated beta-cell.

4/3,AB/6
DIALOG(R)File 155:MEDLINE(R)

13770777 PMID: 11914369
The WNT7b promoter is regulated by TTF-1, GATA6, and Foxa2 in lung epithelium.

Weidenfeld Joel; Shu Weiguo; Zhang Lili; Millar Sarah E; Morrisey Edward E
Department of Medicine, Molecular Cardiology Research Center, and the Department of Dermatology, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.

Journal of biological chemistry (United States) Jun 7 2002, 277 (23) p21061-70, ISSN 0021-9258--Print Journal Code: 2985121R
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

In this study, we find that WNT7b is the only member of the WNT family of autocrine/paracrine signaling molecules whose expression in the lung is restricted to the airway epithelium during embryonic development. To study the transcriptional mechanisms that underlie this restricted pattern of WNT7b expression, we isolated the proximal 1.0-kb mouse WNT7b promoter and mapped the transcriptional start sites. Transfection of the lung epithelial cell line MLE-15, which expresses WNT7b, shows that the 1.0-kb mouse WNT7b promoter is highly active in lung epithelial cells. This region of the WNT7b promoter contains several DNA binding sites for the important lung-restricted transcription factors TTF-1, GATA6, and Foxa2. Electrophoretic mobility shift assays showed that TTF-1, GATA6, and Foxa2 can bind to a specific subset of their consensus DNA binding sites within the WNT7b promoter. Using cotransfection assays, we demonstrate that TTF-1, GATA6, and Foxa2 can trans-activate the WNT7b promoter in NIH-3T3 cells. Truncation of GATA6 or Foxa2 binding sites reduced the ability of these transcriptional regulators to trans-activate the WNT7b promoter. Finally, the minimal 118-bp region of the mouse WNT7b promoter containing only TTF-1 binding sites was synergistically activated by TTF-1 and GATA6, and we show that TTF-1 and GATA6 physically interact in vivo. Together, these results

suggest that WNT7b gene expression in the lung epithelium is regulated in a combinatorial fashion by TTF-1, GATA6, and Foxa2.

4/3,AB/7
DIALOG(R)File 155:MEDLINE(R)

13741561 PMID: 11875061
Foxa2 (HNF3beta) controls multiple genes implicated in metabolism-secretion coupling of glucose-induced insulin release.
Wang Haiyan; Gauthier Benoit R; Hagenfeldt-Johansson Kerstin A; Iezzi Mariella; Wollheim Claes B
Division of Clinical Biochemistry, Department of Internal Medicine, University Medical Center, CH-1211 Geneva 4, Switzerland. Haiyan.Wang@medicine.unige.ch
Journal of biological chemistry (United States) May 17 2002, 277 (20) p17564-70, ISSN 0021-9258--Print Journal Code: 2985121R
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The transcription factor Foxa2 is implicated in blood glucose homeostasis. Conditional expression of Foxa2 or its dominant-negative mutant DN-Foxa2 in INS-1 cells reveals that Foxa2 regulates the expression of genes important for glucose sensing in pancreatic beta-cells. Overexpression of Foxa2 results in blunted glucose-stimulated insulin secretion, whereas induction of DN-Foxa2 causes a left shift of glucose-induced insulin release. The mRNA levels of GLUT2 and glucokinase are drastically decreased after induction of Foxa2. In contrast, loss of Foxa2 function leads to up-regulation of hexokinase (HK) I and II and glucokinase (HK-IV) mRNA expression. The glucokinase and the low K(m) hexokinase activities as well as glycolysis are increased proportionally. In addition, induction of DN-Foxa2 also reduces the expression of beta-cell K(ATP) channel subunits Sur1 and Kir6.2 by 70%. Furthermore, in contrast to previous reports, induction of Foxa2 causes pronounced decreases in the HNF4alpha and HNF1alpha mRNA levels. Foxa2 fails to regulate the expression of Pdx1 transcripts. The expression of insulin and islet amyloid polypeptide is markedly suppressed after induction of Foxa2, while the glucagon mRNA levels are significantly increased. Conversely, Foxa2 is required for glucagon expression in these INS-1-derived cells. These results suggest that Foxa2 is a vital transcription factor evolved to control the expression of genes essential for maintaining beta-cell glucose sensing and glucose homeostasis.

4/3,AB/8
DIALOG(R)File 155:MEDLINE(R)

13631653 PMID: 11846474
Maintenance of the specification of the anterior definitive endoderm and forebrain depends on the axial mesendoderm: a study using HNF3beta/ Foxa2 conditional mutants.
Hallonet Marc; Kaestner Klaus H; Martin-Parras Luis; Sasaki Hiroshi; Betz Ulrich A K; Ang Siew-Lan
Institut de Genetique et de Biologie Moleculaire et Cellulaire, CNRS/INSERM/Universite Louis Pasteur, C.U. de Strasbourg, Illkirch, France.
Developmental biology (United States) Mar 1 2002, 243 (1) p20-33, ISSN 0012-1606--Print Journal Code: 0372762
Publishing Model Print
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

In mouse embryo, the early induction of the head region depends on signals from the anterior visceral endoderm (AVE) and the anterior primitive streak. Subsequently, node derivatives, including anterior definitive endoderm and axial mesendoderm, are thought to play a role in the maintenance and elaboration of anterior neural character. Foxa2 encodes a winged-helix transcription factor expressed in signaling centers required for head development, including the AVE, anterior primitive streak, anterior definitive endoderm, and axial mesendoderm. To address Foxa2 function during formation of the head, we used conditional mutants in which Foxa2 function is preserved in extraembryonic tissues during early embryonic stages and inactivated in embryonic tissues after the onset of gastrulation. In Foxa2 conditional mutants, the anterior neural plate and anterior definitive endoderm were initially specified. In contrast, the axial mesendoderm failed to differentiate. At later stages, specification of the anterior neural plate and anterior definitive endoderm was shown to be labile. As a result, head truncations were observed in Foxa2 conditional mutants. Our results therefore indicate that anterior definitive endoderm alone is not sufficient to maintain anterior head specification and that an interaction between the axial mesendoderm and the anterior definitive endoderm is required for proper specification of the endoderm. Foxa2 therefore plays an integral role in the formation of axial mesendoderm, which is required to maintain the specification of the forebrain and the anterior definitive endoderm.

4/3,AB/9
DIALOG(R)File 155:MEDLINE(R)

13577837 PMID: 11773447

Hepatic nuclear factor-3 (HNF-3 or Foxa2) regulates glucagon gene transcription by binding to the G1 and G2 promoter elements.

Gauthier Benoit R; Schwitzgebel Valerie M; Zaiko Maia; Mamin Aline; Ritz-Laser Beate; Philippe Jacques

Unite de Diabetologie Clinique, Centre Medical Universitaire, 1211 Geneve 4, Switzerland. benoit.gauthier@medecine.unige.ch

Molecular endocrinology (Baltimore, Md.) (United States) Jan 2002, 16 (1) p170-83, ISSN 0888-8809--Print Journal Code: 8801431

Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Glucagon gene expression in the endocrine pancreas is controlled by three islet-specific elements (G3, G2, and G4) and the alpha-cell-specific element G1. Two proteins interacting with G1 have previously been identified as Pax6 and Cdx2/3. We identify here the third yet uncharacterized complex on G1 as hepatocyte nuclear factor 3 (HNF-3)beta, a member of the HNF-3/forkhead transcription family, which plays an important role in the development of endoderm-related organs. HNF-3 has been previously demonstrated to interact with the G2 element and to be crucial for glucagon gene expression; we thus define a second binding site for this transcription on the glucagon gene promoter. We demonstrate that both HNF-3alpha and -beta produced in heterologous cells can interact with similar affinities to either the G1 or G2 element. Pax6, which binds to an overlapping site on G1, exhibited a greater affinity as compared with HNF-3alpha or -beta. We show that both HNF-3beta and -alpha can transactivate glucagon gene transcription through the G2 and G1 elements. However, HNF-3 via its transactivating domains specifically impaired Pax6-mediated transactivation of the glucagon promoter but had no effect on

transactivation by Cdx2/3. We suggest that HNF-3 may play a dual role on glucagon gene transcription by 1) inhibiting the transactivation potential of Pax6 on the G1 and G3 elements and 2) direct activation through G1 and G2.

4/3,AB/10
DIALOG(R)File 155:MEDLINE(R)

13293248 PMID: 11445544
Tissue-specific deletion of Foxa2 in pancreatic beta cells results in hyperinsulinemic hypoglycemia.
Sund N J; Vatamaniuk M Z; Casey M; Ang S L; Magnuson M A; Stoffers D A; Matschinsky F M; Kaestner K H
Department of Genetics, Penn Diabetes Center, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA.
Genes & development (United States) Jul 1 2001, 15 (13) p1706-15, ISSN 0890-9369--Print Journal Code: 8711660
Contract/Grant No.: 5-T32-GM08216; GM; NIGMS; P30 DK19525; DK; NIDDK; P30 DK50306; DK; NIDDK; PO1 DK55342; DK; NIDDK
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
We have used conditional gene ablation to uncover a dramatic and unpredicted role for the winged-helix transcription factor Foxa2 (formerly HNF-3 beta) in pancreatic beta-cell differentiation and metabolism. Mice that lack Foxa2 specifically in beta cells (Foxa2(loxP/loxP); Ins.Cre mice) are severely hypoglycemic and show dysregulated insulin secretion in response to both glucose and amino acids. This inappropriate hypersecretion of insulin in the face of profound hypoglycemia mimics pathophysiological and molecular aspects of familial hyperinsulinism. We have identified the two subunits of the beta-cell ATP-sensitive K(+) channel (K(ATP)), the most frequently mutated genes linked to familial hyperinsulinism, as novel Foxa2 targets in islets. The Foxa2(loxP/loxP); Ins.Cre mice will serve as a unique model to investigate the regulation of insulin secretion by the beta cell and suggest the human FOXA2 as a candidate gene for familial hyperinsulinism.

4/3,AB/11
DIALOG(R)File 155:MEDLINE(R)

13163319 PMID: 11287181
Identification of essential sequence motifs in the node/notochord enhancer of Foxa2 (Hnf3beta) gene that are conserved across vertebrate species.
Nishizaki Y; Shimazu K; Kondoh H; Sasaki H
Laboratory of Developmental Biology, Institute for Molecular and Cellular Biology, Osaka University, 1-3 Yamada-oka, Suita, 565-0871, Osaka, Japan.
Mechanisms of development (Ireland) Apr 2001, 102 (1-2) p57-66, ISSN 0925-4773--Print Journal Code: 9101218
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The expression of a winged-helix transcription factor, Foxa2/HNF3beta, is essential for development of the node and the notochord. We examined the node/notochord enhancer of mouse Foxa2 for sequence motifs conserved across

vertebrate species. We cloned Foxa2 genes from chicken and fish, and identified the respective node/notochord enhancers that were active in transgenic mouse embryos. Comparison of the sequences of the enhancers revealed three evolutionally conserved sequence motifs, CS1, CS2 and CS3. Mutational analysis of the mouse enhancer indicated that CS3 is indispensable for gene expression in the node and the notochord, while CS1 and CS2 are required to augment enhancer activity. These motifs do not correspond to the consensus binding sequences of transcription factors known to be involved in node/notochord development.

4/3,AB/12
DIALOG(R)File 155:MEDLINE(R)

12759852 PMID: 10866673
Hepatocyte nuclear factor 3beta (Foxa2) is dispensable for maintaining the differentiated state of the adult hepatocyte.
Sund N J; Ang S L; Sackett S D; Shen W; Daigle N; Magnuson M A; Kaestner K H
Department of Genetics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104-6145, USA.
Molecular and cellular biology (UNITED STATES) Jul 2000, 20 (14) p5175-83, ISSN 0270-7306--Print Journal Code: 8109087
Contract/Grant No.: P30 DK50306; DK; NIDDK; RO1 DK42502; DK; NIDDK; RO1 DK53342; DK; NIDDK; +
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Liver-specific gene expression is controlled by a heterogeneous group of hepatocyte-enriched transcription factors. One of these, the winged helix transcription factor hepatocyte nuclear factor 3beta (HNF3beta or Foxa2) is essential for multiple stages of embryonic development. Recently, HNF3beta has been shown to be an important regulator of other hepatocyte-enriched transcription factors as well as the expression of liver-specific structural genes. We have addressed the role of HNF3beta in maintenance of the hepatocyte phenotype by inactivation of HNF3beta in the liver. Remarkably, adult mice lacking HNF3beta expression specifically in hepatocytes are viable, with histologically normal livers and normal liver function. Moreover, analysis of >8,000 mRNAs by array hybridization revealed that lack of HNF3beta affects the expression of only very few genes. Based on earlier work it appears that HNF3beta plays a critical role in early liver development; however, our studies demonstrate that HNF3beta is not required for maintenance of the adult hepatocyte or for normal liver function. This is the first example of such functional dichotomy for a tissue specification transcription factor.

```
? s admins?(2n)foxa2
             367  ADMINS?
             363  FOXA2
      S5       0  ADMINS?(2N)FOXA2
? s admin?(2n)foxa2
         1615035  ADMIN?
             363  FOXA2
      S6       0  ADMIN?(2N)FOXA2
? ds

Set      Items   Description
S1         363   FOXA2 OR FOX()A2
S2          37   (FOXA2 OR FOX()A2)/TI
S3          25   S2 AND PY>2003
S4          12   S2 NOT S3
```

10/614481 09/07/2006

```
S5            0   ADMINS?(2N)FOXA2
S6            0   ADMIN?(2N)FOXA2
? s s1 and (therapy or therapeutic)
              363  S1
          2582940  THERAPY
          1543069  THERAPEUTIC
      S7        9  S1 AND (THERAPY OR THERAPEUTIC)
? s s1 and (therapy or therapeutic or administration)
              363  S1
          2582940  THERAPY
          1543069  THERAPEUTIC
          1442501  ADMINISTRATION
      S8       17  S1 AND (THERAPY OR THERAPEUTIC OR ADMINISTRATION)
? s s8 not s4
               17  S8
               12  S4
      S9       17  S8 NOT S4
? t s9/3,ab/all

 9/3,AB/1
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

23463097   PMID: 17304540
   System for inducible expression of cre-recombinase from the Foxa2
 locus in endoderm, notochord, and floor plate.
  Frank Deborah U; Elliott Sarah A; Park Eon Joo; Hammond Jennetta; Saijoh
Yukio; Moon Anne M
  Department of Pediatrics, University of Utah School of Medicine, Salt
Lake City, Utah, USA.
  Developmental dynamics - an official publication of the American
Association of Anatomists (United States) Apr 2007, 236 (4) p1085-92,
ISSN 1058-8388--Print Journal Code: 9201927
  Contract/Grant No.: R01HD044157-01; HD; NICHD
  Publishing Model Print
  Document type: Journal Article; Research Support, N.I.H., Extramural;
Research Support, Non-U.S. Gov't
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: In Process
  We targeted the reverse tetracycline controlled transactivator (rtTA) to
the Foxa2 locus (Foxa2 (ITA)) to generate a system for
regulating Cre-recombinase activity within Foxa2 expression domains,
including the endoderm, notochord, and floor plate of early mouse embryos.
The use of an internal ribosomal entry site to obtain rtTA expression
preserves Foxa2 function of the targeted allele. Cre activity with
this system reflects the level of endogenous Foxa2 activity and is
also tightly controlled by doxycycline. The location of Cre activity within
the broader Foxa2 expression domain can be restricted by altering the
timing of doxycycline administration. Isolated floor plate expression
can be obtained in this manner. This system will provide a useful tool for
manipulating gene expression in endoderm, notochord, and floor plate, all
of which are tissues with important structural and patterning functions
during embryogenesis.


 9/3,AB/2
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

23438772   PMID: 17283222
  The hepatocyte nuclear factor 6 (HNF6) and FOXA2 are key regulators
in colorectal liver metastases.
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Lehner F; Kulik U; Klempnauer J; Borlak J
Department of General, Visceral and Transplantation Surgery, Hannover Medical School, Hannover, Germany.
FASEB journal - official publication of the Federation of American Societies for Experimental Biology (United States) May 2007, 21 (7) p1445-62, ISSN 1530-6860--Electronic Journal Code: 8804484
Publishing Model Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
The molecular causes leading to secondary liver malignancies are unknown. Here we report regulation of major hepatic nuclear factors in human colorectal liver metastases and primary colonic cancer. Notably, the genes coding for HNF6, HNF1beta, and C/EBPgamma were selectively regulated in liver metastases. We therefore studied protein expression of regulated transcription factors and found unacetylated HNF6 to be a hallmark of colorectal liver metastases. For its known interaction with HNF6, we investigated expression of FOXA2, which we found to be specifically induced in colorectal liver metastases. By electromobility shift assay, we examined DNA binding of disease regulated transcription factors. Essentially, no HNF6 DNA binding was observed. We also searched for sequence variations in the DNA binding domains of HNF6, but did not identify any mutation. Furthermore, we probed for expression of 28 genes targeted by HNF6. Mostly transcript expression was repressed except for tumor growth. In conclusion, we show HNF6 protein expression to be driven by the hepatic environment. Its expression is not observed in healthy colon or primary colonic cancer. HNF6 DNA binding is selectively abrogated through lack of post-translational modification and interaction with FOXA2. Targeting of FOXA2 and HNF6 may therefore enable mechanism-based therapy for colorectal liver metastases.

23364093 PMID: 17299990
Instant hepatic differentiation of human embryonic stem cells using activin A and a deleted variant of HGF.
Chen Yong; Soto-Gutierrez Alejandro; Navarro-Alvarez Nalu; Rivas-Carrillo Jorge David; Yamatsuji Tomoki; Shirakawa Yasuhiro; Tanaka Noriaki; Kobayashi Naoya
Department of Surgery, Okayama University Graduate School of Medicine and Dentistry, Okayama 700-8558, Japan.
Cell transplantation (United States) 2006, 15 (10) p865-71, ISSN 0963-6897--Print Journal Code: 9208854
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Human embryonic stem (hES) cells have the ability to differentiate into a variety of different cell lineages and potentially provide a source of differentiated cells for many therapeutic uses. Here we investigated an efficient method of hepatic differentiation from hES cells. A human ES cell line, KhES-1, was used and maintained by a nonfeeder method. KhES-1 cells were cultured for 5 days in the presence of human activin A (50 ng/ml) and then treated with a deleted variant of hepatocyte growth factor (dHGF) at 0, 100, or 500 ng/ml for 7 days. The resultant cells were biologically analyzed. The expression of the endodermal genes SOX17 and FOXA2 increased in KhES-1 cells after activin A treatment. In contrast, Oct4, a self-renewal undifferentiated marker, decreased in a

time-dependent manner in KhES-1 cells. Following a 7-day treatment of the resultant cells with dHGF, especially at 500 ng/ml, KhES-1 cells showed an expression of the hepatic makers albumin, AFP, and CK18. Transitional electron microscopy showed well-developed glycogen rosettes and a gap junction in KhES-1 cells treated with 500 ng/ml of dHGF. We developed an efficient method to differentiate KhES-1 cells into hepatocyte-like cells in vitro using 50 ng/ml of activin A and 500 ng/ml of dHGF.

9/3,AB/4
DIALOG(R)File 155:MEDLINE(R)

22996697 PMID: 16410542
Identification of transcriptional targets during pancreatic growth after partial pancreatectomy and exendin-4 treatment.
De Leon Diva D; Farzad Cyrus; Crutchlow Michael F; Brestelli John; Tobias John; Kaestner Klaus H; Stoffers Doris A
Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, Institute for Diabetes, Obesity and Metabolism, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA.
Physiological genomics (United States) Jan 12 2006, 24 (2) p133-43, ISSN 1531-2267--Electronic Journal Code: 9815683
Contract/Grant No.: F32-DK-60273; DK; NIDDK; K12-DK-063682-02; DK; NIDDK; P30-DK-50306; DK; NIDDK; R01-DK-062965; DK; NIDDK; U01-DK-56947; DK; NIDDK
Publishing Model Print
Document type: Journal Article; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
After partial pancreatectomy (Ppx), substantial regeneration of the endocrine and exocrine pancreatic compartments has been shown in adult rodents. Exendin-4 (Ex-4) is a glucagon-like peptide-1 receptor agonist that augments endocrine beta-cell mass by stimulating neogenesis, proliferation, and cell survival. After Ppx, treatment with Ex-4 ameliorates hyperglycemia by stimulating beta-cell mass recovery. We utilized a cDNA microarray approach to identify genes differentially regulated during pancreatic regeneration after Ppx and/or Ex-4 administration . The pancreatic remnant after Ppx showed a large number of differentially regulated genes. In contrast, Ex-4 treatment resulted in a smaller number of differentially regulated genes. Of note, a common subset of genes regulated by Ex-4 and after Ppx was identified, including three members of the mitogenic Reg gene family, Reg2, -3gamma, and -3beta, as well as fragilis, a gene that maintains pluripotency during germ cell specification, and Serpin b1a, a member of an intracellular protease inhibitor family involved in cell survival. These observations were confirmed by real-time PCR. We determined that Reg3beta protein is also induced in the acinar pancreas after Ppx, suggesting a novel role for this factor in pancreatic growth or response to injury. Finally, comparison of transcription factor-binding sites present in the proximal promoters of these genes identified potential common transcription factors that may regulate these genes. Chromatin immunoprecipitation analyses confirmed Reg3gamma as a novel transcriptional target of Foxa2 (HNF3beta). Our data suggest molecular pathways that may regulate pancreatic growth and offer a unique set of candidate genes to target in the development of therapies aimed at improving pancreatic growth and function.

9/3,AB/5
DIALOG(R)File 155:MEDLINE(R)

10/614481 09/07/2006

22951726 PMID: 16980555
IL-13 and epidermal growth factor receptor have critical but distinct roles in epithelial cell mucin production.
Zhen Guohua; Park Sung Woo; Nguyenvu Louis T; Rodriguez Madeleine W; Barbeau Rebecca; Paquet Agnes C; Erle David J
Department of Medicine, University of California, San Francisco, CA 94143-2922, USA.
American journal of respiratory cell and molecular biology (United States) Feb 2007, 36 (2) p244-53, ISSN 1044-1549--Print Journal Code: 8917225
Contract/Grant No.: HL56835; HL; NHLBI; HL72301; HL; NHLBI; HL85089; HL; NHLBI
Publishing Model Print-Electronic
Document type: Journal Article; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Overproduction of mucus is a central feature of asthma. The cytokine, IL-13, epidermal growth factor receptor (EGFR), and transcription factor, FOXA2 , have each been implicated in mucus production, but the mechanistic relationships between these molecules are not yet well understood. To address this, we established a primary normal human bronchial epithelial cell culture system with IL-13-induced mucus production and gene transcript expression changes similar to those seen in vivo in mice. IL-13 did not stimulate release of the EGFR ligand, transforming growth factor (TGF)-alpha. However, there was constitutive release of TGF-alpha from normal human bronchial epithelial cells, and inhibition of TGF-alpha or EGFR reduced both constitutive and IL-13-induced mucin production. Microarray analysis revealed that IL-13 and the EGFR pathway appear to have almost completely independent effects on transcript expression. IL-13 induced a relatively small set of transcripts, including several novel transcripts that might play a role in pathogenesis of allergic airway disease. In contrast, EGFR activity had extensive effects, including altered expression of many transcripts associated with cell metabolism, survival, transcription, and differentiation. One of the few common effects of IL-13 and EGFR signaling was decreased expression of FOXA2 , which is known to prevent mucus production. We conclude that the IL-13 and EGFR pathways make critical but quite distinct contributions to gene regulation in airway epithelial cells, and that both pathways affect expression of the key transcription factor, FOXA2, a known regulator of mucus production.

9/3,AB/6
DIALOG(R)File 155:MEDLINE(R)

21164678 PMID: 16001449
Expression and role of Foxa proteins in prostate cancer.
Mirosevich Janni; Gao Nan; Gupta Aparna; Shappell Scott B; Jove Richard; Matusik Robert J
Vanderbilt Prostate Cancer Center, AA-1302 Medical Center North, Nashville, Tennessee 37232-2765, USA.
Prostate (United States) Jul 1 2006, 66 (10) p1013-28, ISSN 0270-4137--Print Journal Code: 8101368
Contract/Grant No.: R01 AG023490-01; AG; NIA; R01 CA76142-06; CA; NCI; R01 DK55748-05; DK; NIDDK
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

The molecular mechanism(s) for prostate cancer progression to androgen independence are poorly understood. We have recently shown that Foxa1 and Foxa2 proteins are differentially expressed in epithelial cells during murine prostate development, growth, and adult function. Currently, the role of Foxa proteins in prostate cancer development and progression is unknown. Foxa protein expression was investigated in the LPB-Tag LADY mouse prostate cancer models, in human prostate cancer specimens, and various prostate cancer cell lines using Western blot and immunostaining analysis. In vitro transient transfection, studies were performed to investigate Foxa/prostate-specific gene regulation. Foxa1 was strongly expressed in areas of prostatic intraepithelial neoplasia (PIN) in both the androgen dependent 12T-7f and in the metastatic, androgen independent 12T-10 LADY models. Prominent Foxa1 and Foxa2 expression was observed in 12T-10 invasive undifferentiated neuroendocrine carcinomas, in the hormone independent and metastasizing 12T-10 derived, NE-10 allograft tumors, and in all metastatic lesions isolated from 12T-10 mice. Foxa1 protein expression was always observed in human prostate carcinomas, regardless of Gleason grade score, while Foxa2 was only detected in neuroendocrine small cell carcinomas and in some high Gleason score adenocarcinomas. Foxa proteins were also differentially expressed in three prostate cancer cell lines. Importantly, in vitro functional assays demonstrated that Foxa2 could activate androgen-dependent prostate-specific genes in an androgen receptor and ligand-independent manner. These results suggest that Foxa proteins are important in prostate carcinogenesis. In particular, Foxa2 may be involved in progression of prostate cancer to androgen independence. As such, Foxa proteins may represent novel targets for therapeutic intervention.

9/3,AB/7
DIALOG(R)File 155:MEDLINE(R)

19417224 PMID: 16186387

Signals from the embryonic mouse pancreas induce differentiation of human embryonic stem cells into insulin-producing beta-cell-like cells.

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Diabetes (United States) Oct 2005, 54 (10) p2867-74, ISSN 0012-1797 --Print Journal Code: 0372763

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

The recent success in restoring normoglycemia in type 1 diabetes by islet cell transplantation indicates that cell replacement therapy of this severe disease is achievable. However, the severe lack of donor islets has increased the demand for alternative sources of beta-cells, such as adult and embryonic stem cells. Here, we investigate the potential of human embryonic stem cells (hESCs) to differentiate into beta-cells. Spontaneous differentiation of hESCs under two-dimensional growth conditions resulted in differentiation of Pdx1(+)/Foxa2 (+) pancreatic progenitors and Pdx1(+)/Isl1(+) endocrine progenitors but no insulin-producing cells. However, cotransplantation of differentiated hESCs with the dorsal pancreas, but not with the liver or telencephalon, from mouse embryos resulted in differentiation of beta-cell-like cell clusters. Comparative analysis of the basic characteristics of hESC-derived insulin(+) cell clusters with human adult islets demonstrated that the insulin(+) cells share important features with normal beta-cells, such as synthesis (proinsulin) and processing (C-peptide) of insulin and nuclear localization of key beta-cell transcription factors, including Foxa2, Pdx1, and

Isl1.

9/3,AB/8
DIALOG(R)File 155:MEDLINE(R)

15499469 PMID: 15949766
Does chasing selected 'Fox' to the nucleus prevent diabetes?
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Trends in molecular medicine (England) Jun 2005, 11 (6) p262-5, ISSN 1471-4914--Print Journal Code: 100966035
Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Foxa2 (Hnf3beta) is a winged-helix/forkhead transcription factor that regulates gene expression in the liver, pancreatic islets and adipocytes. It is required for the maintenance of glucose and lipid homeostasis. Hyperinsulinemia-mediated inactivation of Foxa2 by nuclear exclusion has recently been implicated in the development of liver steatosis and insulin resistance in three animal models of diabetes. These abnormalities were cured by adenovirus-mediated expression of a constitutively active form of Foxa2 containing a mutated T156 phosphorylation site, which increases fatty acid oxidation and reduces its biosynthesis. Accordingly, the prevention of phosphorylation of Foxa2 was suggested as a pharmacological target for the treatment of obesity and diabetes.

9/3,AB/9
DIALOG(R)File 155:MEDLINE(R)

15392624 PMID: 15739227
Retinoic acid generated by Raldh2 in mesoderm is required for mouse dorsal endodermal pancreas development.
Molotkov Andrei; Molotkova Natalia; Duester Gregg
OncoDevelopmental Biology Program, Burnham Institute, La Jolla, CA 92037, USA.
Developmental dynamics - an official publication of the American Association of Anatomists (United States) Apr 2005, 232 (4) p950-7, ISSN 1058-8388--Print Journal Code: 9201927
Contract/Grant No.: GM62848; GM; NIGMS
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Studies on nonmammalian vertebrate embryos have indicated that retinoic acid (RA) is required for pancreas development. We have analyzed mouse embryos carrying a null mutation of the gene encoding retinaldehyde dehydrogenase 2 (Raldh2), which controls RA synthesis. Raldh2-/- embryos specifically lack expression of Pdx1 (a homeobox gene required for pancreas development) and Prox1 in dorsal endodermal but not ventral endodermal pancreatic precursor tissues. Ventral endodermal expression of Hex is not affected in Raldh2-/- embryos, indicating that liver specification is not dependent upon RA. Also, expression of Foxa2 across the dorsoventral axis of the endoderm is not affected in Raldh2-/- embryos, indicating that a lack of RA does not cause a general defect in foregut endoderm

development. Comparison of wild-type and Raldh2-/- embryos carrying an RA-reporter transgene demonstrates that RA activity is normally present throughout the endoderm except in the ventral-most region but is totally missing in endoderm of Raldh2-/- embryos. Thus, Raldh2 expressed in adjacent splanchnic lateral plate mesoderm provides an RA signal to dorsal endoderm. Dorsal Pdx1 expression is rescued in Raldh2-/- embryos by low-dose maternal administration of RA, which preferentially restores RA-reporter expression in the dorsal endoderm. Our findings demonstrate a specific role for RA in mouse embryos as a mesodermally synthesized signal needed for dorsal endodermal expression of Pdx1 during development of the dorsal pancreatic lineage. Copyright 2005 Wiley-Liss, Inc.

9/3,AB/10
DIALOG(R)File 155:MEDLINE(R)

15137038 PMID: 15472891

Evidence for a molecular mechanism of teratogenicity of SB-236057, a 5-HT1B receptor inverse agonist that alters axial formation.

Augustine-Rauch Karen A; Zhang Qin J; Leonard Jennifer L; Chadderton Antony; Welsh Michael J; Rami Harshad K; Thompson Mervyn; Gaster Laramie; Wier Patrick J

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Birth defects research. Part A, Clinical and molecular teratology (United States) Oct 2004, 70 (10) p789-807, ISSN 1542-0752--Print
Journal Code: 101155107
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

BACKGROUND: SB-236057 is a potent skeletal teratogen in rodents and rabbits, producing axial and posterior somite malformations in cultured rat embryos. The compound shares some structural similarity to cyclopamine. METHODS: M13 phage display was used to identify amino acid motifs with binding affinity to SB-236057. A 10 microM SB-236057 solution was administered to cultured day 9 postcoitus rat embryos and real-time PCR was conducted at 6 hr posttreatment to evaluate early transcriptional response of axial development genes. Whole-mount in situ hybridization of selected transcripts was conducted on embryos at 48 hr post-compound administration . The rat-enhancer of split protein 1 (r-espl) expression-functional characterization was done by transcriptional expression and morpholino antisense approaches. RESULTS: We identified several amino acid motifs that had high binding affinity to SB-236057-biotin conjugates, one with 100% sequence homology to a region of r-espl, one of the Groucho homologs transcribed by the enhancer of split complex (En[spl]C). SB-236057 repressed expression of r-espl and members of the Notch-En[spl]C pathway. Goosecoid and HNF3-beta, both suspected to associate with Groucho proteins, were also responsive, although expression of another putative binding protein, engrailed-1 (en-1), and other en-1 pathway members was not affected. R-espl mRNA was localized along the axis and antisense inhibition produced similar somite malformations as SB-236057 did. At 48 hr post-SB-236057 or post-r-espl antisense administration, affected embryos demonstrated unchanged sonic hedgehog (shh) expression, however HNF3-beta expression was either absent, altered, or reduced. CONCLUSIONS: We present experimental evidence that the mechanism of SB-236057 teratogenicity includes transcriptional alterations to the Notch1-En[spl] pathway. In addition, alterations in HNF3-beta expression were similar to those induced by cyclopamine. The relationships between r-espl with Notch1 and shh signaling pathways and potential mechanisms of SB-236057 teratogenicity are also discussed. (c) 2004 Wiley-Liss, Inc.

9/3,AB/11
DIALOG(R)File 155:MEDLINE(R)

14907426 PMID: 15166786
New insights into inhibitors of adipogenesis.
Harp Joyce B
Department of Nutrition and Medicine, University of North Carolina, Chapel Hill, NC 27599, USA.
Current opinion in lipidology (England) Jun 2004, 15 (3) p303-7, ISSN 0957-9672--Print Journal Code: 9010000
Contract/Grant No.: DK 53398; DK; NIDDK; DK 56350; DK; NIDDK
Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
PURPOSE OF REVIEW: Adipose tissue is a dynamic organ that changes mass throughout life in response to the metabolic needs of the animal. In the past three decades, significant advances have been made in delineating key extracellular and intracellular stimulators of fat cell formation or adipogenesis. In this review, the author focuses on new findings of specific inhibitors of adipogenesis. Understanding the balance between positive and negative regulators of adipogenesis has important health-related implications for anti-obesity medical therapy and lipodystrophy. RECENT FINDINGS: Adipogenesis is a highly regulated process requiring coordinated expression and activation of two main groups of adipogenic transcription factors, CCAAT/enhancer binding proteins and peroxisome proliferators activated receptor gamma. In response to hormonal and nutrient stimuli, the increased expression and activation of these transcription factors induce the expression of adipocyte-specific genes. More recently, several groups have identified extracellular inhibitors of adipocyte formation, including cytokines, lipid molecules, genistein, and protease inhibitors. Intracellular signaling molecules, which negatively regulate adipogenesis, include Pref-1, Foxo1, Foxa2, SMAD-3, WNT-10b, GATA-2 and GATA-3. SUMMARY: The prevalence of obesity is increasing in the United States and in other westernized societies. Understanding the mechanisms of excessive energy storage in adipose tissue is necessary to develop a comprehensive strategy to prevent and treat obesity. One potential, but unrealized, approach to obesity treatment is to target excessive adipose tissue enlargement. A number of promising extra- and intracellular inhibitors of fat cell formation have been identified, but the modulation of adipose tissue mass may have both advantageous and deleterious health effects.

9/3,AB/12
DIALOG(R)File 155:MEDLINE(R)

14849113 PMID: 15100175
Role of Sp1, C/EBP alpha, HNF3, and PXR in the basal- and xenobiotic-mediated regulation of the CYP3A4 gene.
Bombail Vincent; Taylor Kevin; Gibson G Gordon; Plant Nick
School of Biomedical and Molecular Sciences, University of Surrey, Guildford GU2 7XH, Surrey, United Kingdom.
Drug metabolism and disposition- the biological fate of chemicals (United States) May 2004, 32 (5) p525-35, ISSN 0090-9556--Print Journal Code: 9421550
Publishing Model Print
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Cytochrome P450 3A4 (CYP3A4) is the major cytochrome P450 present in adult human liver and is involved in the metabolism of over 50% of therapeutic compounds currently in use. Since expression levels of CYP3A4 are regulated by many of these compounds, this raises the potential for drug-drug interactions and subsequent altered efficacy or toxicity of the individual compounds at the dose prescribed. Hence, understanding the molecular mechanisms of CYP3A4 regulation is of key importance in predicting and understanding such interactions. To examine this we have used DNase I footprinting and bioinformatic analysis to identify putative transcription factor binding sites within the 250 base pairs of promoter proximal to the transcription start site. We identified several protected fragments within this region that corresponded to putative binding sites for Sp1, AP2, CCAAT/enhancer binding protein (C/EBPalpha), and hepatic nuclear factor-3 (HNF3), as well as confirming previously identified C/EBPalpha, pregnane X receptor (PXR), and HNF3 binding sites. Sequential site-directed mutagenesis of C/EBPalpha, Sp1, HNF3, and PXR binding sites was next used to examine the role of these sites in basal CYP3A4 expression. Disruption of the C/EBPalpha, HNF3, and PXR binding sites all affected basal expression. Finally, the role of these sites was examined in activation of CYP3A4 expression by rifampicin, metyrapone, clotrimazole, and phenobarbital. Disruption of any of these sites either led to an altered pattern of activation by the xenobiotic, as altered maximal activation, or altered the EC(50) value of activation. Such effects were xenobiotic-specific, with each disrupted site playing a role in the activation of some of the xenobiotics.

9/3,AB/13
DIALOG(R)File 155:MEDLINE(R)

14484187 PMID: 12967472

Expression of HNFs and C/EBP alpha is correlated with immunocytochemical differentiation of cell lines derived from human hepatocellular carcinomas, hepatoblastomas and immortalized hepatocytes.

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Department of Pathology, Institute of Basic Medical Sciences, University of Tsukuba, Tsukuba, Ibaraki-shi, Ibaraki 305-8575, Japan.

Cancer science (Japan) Sep 2003, 94 (9) p757-63, ISSN 1347-9032--Print Journal Code: 101168776
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Objective assessment of the differentiation grade of hepatocellular carcinomas (HCCs) is important for evaluation of the pathological diagnosis, prognosis and therapeutic treatment. Differentiation of hepatocytes is reflected by their expression of hepatic functional proteins in the mouse embryo, and liver-enriched transcription factors (LETFs) have been shown to regulate hepatic functional genes strictly. Previous reports demonstrated that the level of LETF expression is altered in HCC or preneoplastic nodules compared with noncancerous tissues. Therefore, LETF expression levels might be useful as a measure of HCC maturation. In this study, to clarify the correlation between the expression of LETFs and the differentiation grade of HCCs, we performed a quantitative analysis of the mRNA expressions of HNFs and C/EBP alpha using real-time reverse-transcription PCR and immunocytochemical analysis for hepatic functional proteins in twelve cell lines. Furthermore, we examined

orthotopic transplantations of the HCC cell lines in C.B-17/Icrj-scid/scid mice and characterized the histologic and cytologic differentiation of the tumors that developed. Our results showed that comprehensive expressions of HNF-3beta, HNF-4 alpha, HNF-1 alpha, and C/EBP alpha were specific to HCCs with well-differentiated function and morphology. Furthermore, among these four transcription factors, HNF-4 alpha and HNF-1 alpha expressions showed synchronism and had a close relation with HCC differentiation. These in vitro results were confirmed in tumors developed in SCID mice in vivo. These findings suggested that HNF-4 alpha and HNF-1 alpha are useful markers to assess the degree of HCC differentiation, which we suggest could be evaluated objectively by the quantitative analysis of HNFs and C/EBP alpha in HCCs.

9/3,AB/14
DIALOG(R)File 155:MEDLINE(R)

13633294 PMID: 11849991
Altered liver gene expression in CCl4-cirrhotic rats is partially normalized by insulin-like growth factor-I.
Mirpuri Eduardo; Garcia-Trevijano Elena R; Castilla-Cortazar Inma; Berasain Carmen; Quiroga Jorge; Rodriguez-Ortigosa Carlos; Mato Jose M; Prieto Jesus; Avila Matias A
Division de Hepatologia y Terapia Genica, Facultad de Medicina, Departamento de Medicina Interna, Universidad de Navarra, 31008, Pamplona, Spain.
international journal of biochemistry & cell biology (England) Mar 2002 , 34 (3) p242-52, ISSN 1357-2725--Print Journal Code: 9508482
Contract/Grant No.: R01 AA-12677; AA; NIAAA
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
We have previously shown that the administration of low doses of insulin-like growth factor-I (IGF-I) to CCl4-cirrhotic rats improves liver function and reduces fibrosis. To better understand the mechanisms behind the hepatoprotective effects of IGF-I, and to identify those genes whose expression is affected in cirrhosis and after IGF-1 treatment, we have performed differential display of mRNA analysis by means of polymerase chain reaction (PCR) in livers from control and CCl4-cirrhotic rats treated or not with IGF-I. We have identified 16 genes that were up- or down-regulated in the cirrhotic liver. IGF-I treatment partially normalized the expression of eight of these genes, including serine proteinase inhibitors such as serpin-2 and alpha-1-antichymotripsin, alpha-1-acid glycoprotein, and alpha-2u-globulin. Additionally, we show that IGF-I enhanced the regenerative activity in the cirrhotic liver, as determined by the increased expression of the proliferating cell nuclear antigen (PCNA). Finally, IGF-I treatment partially restored the expression of growth hormone receptor (GHR) and the levels of global genomic DNA methylation, which are reduced in human and experimental cirrhosis. Taken together, our observations confirm the hepatoprotective effects of IGF-I, and suggest that this action can be exerted in part through the normalization of liver gene expression, growth hormone (GH) responsiveness and global genomic DNA methylation.

9/3,AB/15
DIALOG(R)File 155:MEDLINE(R)

12887223 PMID: 11018767

Gene expression of the three members of hepatocyte nuclear factor-3 is differentially regulated by nutritional and hormonal factors.

Imae M; Inoue Y; Fu Z; Kato H; Noguchi T

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Journal of endocrinology (ENGLAND) Oct 2000, 167 (1) pR1-5, ISSN 0022-0795--Print Journal Code: 0375363

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Hepatocyte nuclear factor-3 (HNF-3) belongs to a large family of forkhead transcription factors and is made up of three members (HNF-3alpha, -3beta and -3gamma). It has been shown that HNF-3 regulates a number of metabolically important genes. However, the mechanisms underlying this regulation of HNF-3 activity by hormones and nutrition have not yet been well elucidated. In attempting to explore the regulation of gene expression of HNF-3 members by physiological status, we analyzed the effects of insulin, dexamethasone and protein malnutrition on the hepatic mRNA level of each member. Male Wistar rats were fed on a 12% casein diet, 12% gluten diet (deficient in lysine and threonine) or a protein-free diet for 1 week. The protein-free diet and gluten diet caused a 3. 7-fold increase in HNF-3g mRNA in the liver and did not affect the mRNA level of either HNF-3alpha or HNF-3beta. Daily administration of dexamethasone caused the mRNA levels of HNF-3alpha and HNF-3beta to increase (2.3- and 1.4-fold, respectively), but had no effect on the HNF-3gamma mRNA level. In diabetic rats that had been injected with streptozotocin, an elevation of the hepatic mRNA levels of HNF-3beta and HNF-3gamma was observed (1.6-and 1.9-fold, respectively). Insulin replacement in the diabetic rats decreased both mRNA levels in a dose-dependent manner. HNF-3alpha mRNA was not affected by insulin status. These results show that the genes of the three members of the HNF-3 family respond differently to hormonal and nutritional factors suggesting that the activities of HNF-3 members are regulated, at least in part, by the levels of their gene expression.

9/3,AB/16

11731738 PMID: 9535920

Estrogen regulation of the apolipoprotein AI gene promoter through transcription cofactor sharing.

Harnish D C; Evans M J; Scicchitano M S; Bhat R A; Karathanasis S K

Department of Nuclear Receptors, Wyeth-Ayerst Research, Radnor, Pennsylvania 19087, USA.

Journal of biological chemistry (UNITED STATES) Apr 10 1998, 273 (15) p9270-8, ISSN 0021-9258--Print Journal Code: 2985121R

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Estrogen replacement therapy increases plasma concentrations of high density lipoprotein and its major protein constituent, apolipoprotein AI (apoAI). Studies with animal model systems, however, suggest opposite effects. In HepG2 cells stably expressing estrogen receptor alpha (ERalpha), 17beta-estradiol (E2) potently inhibited apoAI mRNA steady state levels. ApoAI promoter deletion mapping experiments indicated that ERalpha plus E2 inhibited apoAI activity through the liver-specific enhancer. Although the ERalpha DNA binding domain was essential but not sufficient

for apoAI enhancer inhibition, ERalpha binding to the apoAI enhancer could not be detected by electrophoretic mobility shift assays. Western blotting and cotransfection assays showed that ERalpha plus E2 did not influence the abundance or the activity of the hepatocyte-enriched factors HNF-3beta and HNF-4, two transcription factors essential for apoAI enhancer function. Expression of the ERalpha coactivator RIP140 dramatically repressed apoAI enhancer function in cotransfection experiments, suggesting that RIP140 may also function as a coactivator on the apoAI enhancer. Moreover, estrogen regulation of apoAI enhancer activity was dependent upon the balance between ERalpha and RIP140 levels. At low ratios of RIP140 to ERalpha, E2 repressed apoAI enhancer activity, whereas at high ratios this repression was reversed. Regulation of the apoAI gene by estrogen may thus vary in direction and magnitude depending not only on the presence of ERalpha and E2 but also upon the intracellular balance of ERalpha and coactivators utilized by ERalpha and the apoAI enhancer.

9/3,AB/17
DIALOG(R)File 155:MEDLINE(R)

10893084 PMID: 8662915
Control of apolipoprotein AI gene expression through synergistic interactions between hepatocyte nuclear factors 3 and 4.
Harnish D C; Malik S; Kilbourne E; Costa R; Karathanasis S K
Department of Cardiovascular Molecular Biology, Lederle Laboratories, Pearl River, New York 10965, USA.
Journal of biological chemistry (UNITED STATES) Jun 7 1996, 271 (23) p13621-8, ISSN 0021-9258--Print Journal Code: 2985121R
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Apolipoprotein AI (apoAI) gene expression in liver depends on synergistic interactions between transcription factors bound to three distinct sites (A, B, and C) within a hepatocyte-specific enhancer in the 5'-flanking region of the gene. In this study, we showed that a segment spanning sites A and B retains substantial levels of enhancer activity in hepatoblastoma HepG2 cells and that sites A and B are occupied by the liver-enriched hepatocyte nuclear factors (HNFs) 4 and 3, respectively, in these cells. In non-hepatic CV-1 cells, HNF-4 and HNF-3beta activated this minimal enhancer synergistically. This synergy was dependent upon simultaneous binding of these factors to their cognate sites, but it was not due to cooperativity in DNA binding. Separation of these sites by varying helical turns of DNA did not affect simultaneous binding of HNF-3beta and HNF-4 nor did it influence their functional synergy. The synergy was, however, dependent upon the cell type used for functional analysis. In addition, this synergy was further potentiated by estrogen treatment of cells cotransfected with the estrogen receptor. These data indicate that a cell type-restricted intermediary factor jointly recruited by HNF-4 and HNF-3 participates in activation of the apoAI enhancer in liver cells and suggest that the activity of this factor is regulated by estrogen.
? ds

Set	Items	Description
S1	363	FOXA2 OR FOX()A2
S2	37	(FOXA2 OR FOX()A2)/TI
S3	25	S2 AND PY>2003
S4	12	S2 NOT S3
S5	0	ADMINS?(2N)FOXA2
S6	0	ADMIN?(2N)FOXA2
S7	9	S1 AND (THERAPY OR THERAPEUTIC)

10/614481 09/07/2006

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S8          17   S1 AND (THERAPY OR THERAPEUTIC OR ADMINISTRATION)
S9          17   S8 NOT S4
? s s2 and s3
               37  S2
               25  S3
     S10       25  S2 AND S3
? s s3 not s10
               25  S3
               25  S10
     S11        0  S3 NOT S10
? s s3 not s9
               25  S3
               17  S9
     S12       23  S3 NOT S9
? t s12/3,ab/all
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12/3,AB/1
DIALOG(R)File 155:MEDLINE(R)

23492514 PMID: 17267396

Nuclear pregnane X receptor cross-talk with FoxA2 to mediate drug-induced regulation of lipid metabolism in fasting mouse liver.

Nakamura Kouichi; Moore Rick; Negishi Masahiko; Sueyoshi Tatsuya
Pharmacogenetics Section, Laboratory of Reproductive and Developmental Toxicology, NIEHS, National Institutes of Health, Research Triangle Park, North Carolina 27709, USA.

Journal of biological chemistry (United States) Mar 30 2007, 282 (13) p9768-76, ISSN 0021-9258--Print Journal Code: 2985121R
Publishing Model Print-Electronic
Document type: Journal Article; Research Support, N.I.H., Intramural
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Upon drug activation, the nuclear pregnane X receptor (PXR) regulates not only hepatic drug but also energy metabolism. Using Pxr(-/-) mice, we have now investigated the PXR-mediated repression of lipid metabolism in the fasting livers. Treatment with PXR activator pregnenolone 16alpha-carbonitrile (PCN) down-regulated the mRNA levels of carnitine palmitoyltransferase 1A (in beta-oxidation) and mitochondrial 3-hydroxy-3-methylglutarate-CoA synthase 2 (in ketogenesis) in wild-type (Pxr(+/+)) mice only. In contrast, the stearoyl-CoA desaturase 1 (in lipogenesis) mRNA was up-regulated in the PCN-treated Pxr(+/+) mice. Reflecting these up- and down-regulations and consistent with decreased energy metabolism, the levels of hepatic triglycerides and of serum 3-hydroxybutylate were increased and decreased, respectively, in the PCN-treated Pxr(+/+) mice. Using gel shift, glutathione S-transferase pull-down and cell-based reporter assays, we then examined whether PXR could cross-talk with the insulin response forkhead factor FoxA2 to repress the transcription of the Cpt1a and Hmgcs2 genes, because FoxA2 activates these genes in fasting liver. PXR directly bound to FoxA2 and repressed its activation of the Cpt1a and Hmgcs2 promoters. Moreover, ChIP assays showed that PCN treatment attenuated the binding of FoxA2 to these promoters in fasting Pxr(+/+) but not Pxr(-/-) mice. These results are consistent with the conclusion that PCN-activated PXR represses FoxA2-mediated transcription of Ctp1a and Hmgcs2 genes in fasting liver.

12/3,AB/2
DIALOG(R)File 155:MEDLINE(R)

23373241 PMID: 17389379

Crucial roles of Foxa2 in mouse anterior-posterior axis polarization via regulation of anterior visceral endoderm-specific genes.

Kimura-Yoshida Chiharu; Tian E; Nakano Hiroshi; Amazaki Saori; Shimokawa Kayo; Rossant Janet; Aizawa Shinichi; Matsuo Isao

Department of Molecular Embryology, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka Prefectural Hospital Organization, Murodo-cho, Izumi, Osaka 594-1101, Japan.

Proceedings of the National Academy of Sciences of the United States of America (United States) Apr 3 2007, 104 (14) p5919-24, ISSN 0027-8424--Print Journal Code: 7505876

Publishing Model Print-Electronic

Document type: Journal Article; Research Support, Non-U.S. Gov't

Languages: ENGLISH

Main Citation Owner: NLM

Record type: In Process

Anterior visceral endoderm (AVE) plays essential roles with respect to anterior-posterior axis development in the early mouse embryo. To assess the genetic cascade involved in AVE formation, the cis-regulatory elements directing expression of vertebrate Otx2 genes in the AVE were analyzed via generation of transgenic mice. Otx2 expression in AVE is regulated directly by the forkhead transcription factor, Foxa2. Moreover, Foxa2 is essential for expression of the Wnt antagonists, Dkk1 and Cerl, in visceral endoderm during the pre- to early streak stages; however, Foxa2 appears to be dispensable for subsequent Dkk1 expression associated with forebrain induction. Thus, we propose that Foxa2 is crucial in early anterior-posterior axis polarization in terms of regulation of expression of AVE-specific genes. These findings provide profound insights into conserved roles of Foxa2 transcription factors in anterior specification throughout the evolution of the chordate body plan.

12/3,AB/3

22263338 PMID: 16675598

The effect of overexpression of Pdx1 and Foxa2 on the differentiation of human embryonic stem cells into pancreatic cells.

Lavon Neta; Yanuka Ofra; Benvenisty Nissim

Department of Genetics, The Hebrew University, Jerusalem 91904, Israel.

Stem cells (Dayton, Ohio) (United States) Aug 2006, 24 (8) p1923-30, ISSN 1066-5099--Print Journal Code: 9304532

Publishing Model Print-Electronic

Document type: Journal Article; Research Support, Non-U.S. Gov't

Languages: ENGLISH

Main Citation Owner: NLM

Record type: In Process

Human embryonic stem cells (HESCs) are pluripotent cells that may serve as a source of cells for transplantation medicine and as a tool to study human embryogenesis. Using genetic manipulation methodologies, we have investigated the potential of HESCs to differentiate into the various pancreatic cell types. We initially created various HESCs carrying the enhanced green fluorescent protein (eGFP) reporter gene under the control of either the insulin promoter or the pancreatic and duodenal homeobox factor-1 (Pdx1) promoter. Our analysis revealed that during the differentiation of HESCs into embryoid bodies (EBs), we could detect green fluorescent cells when eGFP is regulated by Pdx1 promoter but not by insulin promoter. To examine whether we can induce differentiation into pancreatic cells, we have established human embryonic stem cell lines that constitutively express either Pdx1 or the endodermal transcription factor Foxa2. Following differentiation into EBs, the constitutive expression of Pdx1 enhanced the differentiation of HESCs toward pancreatic endocrine and exocrine cell types. Thus, we have demonstrated expression of several

transcription factors that are downstream of Pdx1 and various molecular markers for the different pancreatic cell types. However, the expression of the insulin gene could be demonstrated only when the cells differentiated in vivo into teratomas. We conclude that although overexpression of Pdx1 enhanced expression of pancreatic enriched genes, induction of insulin expression may require additional signals that are only present in vivo.

12/3,AB/4
DIALOG(R)File 155:MEDLINE(R)

21769709 PMID: 16459311
Coactivation of Foxa2 through Pgc-1beta promotes liver fatty acid oxidation and triglyceride/VLDL secretion.
Wolfrum Christian; Stoffel Markus
Laboratory of Metabolic Diseases, The Rockefeller University, 1230 York Avenue, New York, NY 10021, USA.
Cell metabolism (United States) Feb 2006, 3 (2) p99-110, ISSN 1550-4131--Print Journal Code: 101233170
Contract/Grant No.: 2 R01 DK55033-06; DK; NIDDK; U01 HL70524; HL; NHLBI
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Forkhead transcription factor Foxa2 activates genes involved in hepatic lipid metabolism and is regulated by insulin. Activation of Foxa2 in the liver leads to increased oxidation and secretion of fatty acids in the form of triacylglycerols (TAGs), a process impaired in type 2 diabetes. Here, we demonstrate that Foxa2 is coactivated by PPARgamma coactivator beta (Pgc-1beta). Adenoviral expression of Foxa2 and Pgc-1beta in livers of ob/ob mice results in decreased hepatic TAG content and increased plasma TAG concentrations. In addition, the concerted action of Foxa2/Pgc-1beta activates genes in mitochondrial beta oxidation and enhances fatty acid metabolism. Furthermore, Foxa2/Pgc-1beta induce the expression of microsomal transfer protein, thereby increasing apoB-containing VLDL secretion. This process is inhibited by insulin through a Foxa2-dependent mechanism. These data demonstrate that Foxa2/Pgc-1beta regulate hepatic lipid homeostasis by affecting the clearance rate of fatty acids through oxidation and/or secretion of lipids in response to insulin.

12/3,AB/5
DIALOG(R)File 155:MEDLINE(R)

21640468 PMID: 16847327
FoxA2 , Nkx2.2, and PDX-1 regulate islet beta-cell-specific mafA expression through conserved sequences located between base pairs -8118 and -7750 upstream from the transcription start site.
Raum Jeffrey C; Gerrish Kevin; Artner Isabella; Henderson Eva; Guo Min; Sussel Lori; Schisler Jonathan C; Newgard Christopher B; Stein Roland
Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medical Center,723 Light Hall, Nashville, TN 37232, USA.
Molecular and cellular biology (United States) Aug 2006, 26 (15) p5735-43, ISSN 0270-7306--Print Journal Code: 8109087
Contract/Grant No.: 5T32 DK07563; DK; NIDDK; DK50203; DK; NIDDK; P60 DK20593; DK; NIDDK; U01-DK-56047; DK; NIDDK; U19 DK061248; DK; NIDDK
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM

Record type: MEDLINE; Completed

The MafA transcription factor is both critical to islet beta-cell function and has a unique pancreatic cell-type-specific expression pattern. To localize the potential transcriptional regulatory region(s) involved in directing expression to the beta cell, areas of identity within the 5' flanking region of the mouse, human, and rat mafA genes were found between nucleotides -9389 and -9194, -8426 and -8293, -8118 and -7750, -6622 and -6441, -6217 and -6031, and -250 and +56 relative to the transcription start site. The identity between species was greater than 75%, with the highest found between bp -8118 and -7750 (approximately 94%, termed region 3). Region 3 was the only upstream mammalian conserved region found in chicken mafA (88% identity). In addition, region 3 uniquely displayed beta-cell-specific activity in cell-line-based reporter assays. Important regulators of beta-cell formation and function, PDX-1, FoxA2, and Nkx2.2, were shown to specifically bind to region 3 in vivo using the chromatin immunoprecipitation assay. Mutational and functional analyses demonstrated that FoxA2 (bp -7943 to -7910), Nkx2.2 (bp -7771 to -7746), and PDX-1 (bp -8087 to -8063) mediated region 3 activation. Consistent with a role in transcription, small interfering RNA-mediated knockdown of PDX-1 led to decreased mafA mRNA production in INS-1-derived beta-cell lines (832/13 and 832/3), while MafA expression was undetected in the pancreatic epithelium of Nkx2.2 null animals. These results suggest that beta-cell-type-specific mafA transcription is principally controlled by region 3-acting transcription factors that are essential in the formation of functional beta cells.

12/3,AB/6
DIALOG(R)File 155:MEDLINE(R)

21210509 PMID: 16627590

Regulation of the mouse protein targeting to glycogen (PTG) promoter by the FoxA2 forkhead protein and by 3',5'-cyclic adenosine 5'-monophosphate in H4IIE hepatoma cells.

Cheng Alan; Zhang Mei; Crosson Sean M; Bao Zhao Q; Saltiel Alan R

Department of Internal Medicine, Life Sciences Institute, University of Michigan, Ann Arbor, 48109, USA.

Endocrinology (United States) Jul 2006, 147 (7) p3606-12,
ISSN 0013-7227--Print Journal Code: 0375040

Contract/Grant No.: 5R01DK060597; DK; NIDDK; F32DK064551; DK; NIDDK

Publishing Model Print-Electronic

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

The scaffolding protein, protein targeting to glycogen (PTG), orchestrates the signaling of several metabolic enzymes involved in glycogen synthesis. However, little is known concerning the regulation of PTG itself. In this study, we have cloned and characterized the mouse promoter of PTG. We identified multiple FoxA2 binding sites within this region. FoxA2 is a member of the forkhead family of transcription factors that has recently been implicated in the cAMP-dependent regulation of several genes involved in liver metabolism. Using luciferase reporter constructs, we demonstrate that FoxA2 transactivates the PTG promoter in H4IIE hepatoma cells. Nuclear extracts prepared from mouse liver and H4IIE cells were able to bind a FoxA2-specific probe derived within the PTG promoter region. Chromatin immunoprecipitation experiments further demonstrate that FoxA2 binds to the PTG promoter in vivo. Finally, we show that treatment with cAMP analogs activates the PTG promoter and significantly increases PTG levels in H4IIE cells. Our results provide a framework to investigate how additional transcription factors may regulate PTG expression in other cell types.

12/3,AB/7
DIALOG(R)File 155:MEDLINE(R)

21162960 PMID: 16467259
Foxa1 and Foxa2 interact with the androgen receptor to regulate prostate and epididymal genes differentially.
Yu Xiuping; Gupta Aparna; Wang Yongqing; Suzuki Kichiya; Mirosevich Janni ; Orgebin-Crist Marie-Claire; Matusik Robert J
Department of Urologic Surgery, Vanderbilt University School of Medicine, Nashville, TN 37232, USA.
Annals of the New York Academy of Sciences (United States) Dec 2005, 1061 p77-93, ISSN 0077-8923--Print Journal Code: 7506858
Contract/Grant No.: DK55748-05; DK; NIDDK; HD36900; HD; NICHD; R01 AG023490-01; AG; NIA; R01 CA76142-06; CA; NCI
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Previous studies from our group have shown that Foxa1 is expressed in the prostate and interacts with the androgen receptor (AR) to regulate prostate-specific genes such as prostate-specific antigen (PSA) and probasin (PB). We report here that Foxa2 but not Foxa1 is expressed in the epididymis. Further, Foxa2 interacts with the AR to regulate the mouse epididymal retinoic acid binding protein (mE-RABP) gene, an epididymis-specific gene. Binding of Foxa2 to the mE-RABP promoter was confirmed by gel-shift and chromatin immunoprecipitation (ChIP) assays. Overexpression of Foxa2 suppresses androgen activation of the mE-RABP promoter while overexpression of Foxa2 with prostate-specific promoters activates gene expression in an androgen-independent manner. GST pull-down assays determined that both Foxa1 and Foxa2 physically interact with the DNA binding domain of the AR. The interaction between Foxa proteins and AR was further confirmed by gel-shift assays where Foxa protein was recruited to AR binding oligomers even when Foxa binding sites were not present, and AR was recruited to Foxa binding oligomers even in the absence of an AR binding site. Given that Foxa1 and Foxa2 proteins are expressed differentially in the prostate and epididymis, these data suggest that the Foxa proteins have distinct effects on AR-regulated genes in different male reproductive accessory organs.

12/3,AB/8
DIALOG(R)File 155:MEDLINE(R)

20778411 PMID: 16522789
FoxA2 involvement in suppression of protein C, an outcome predictor in experimental sepsis.
Berg David T; Gerlitz Bruce; Sharma Ganesh R; Richardson Mark A; Stephens Eddie J; Grubbs Renee L; Holmes Kimberly C; Fynboe Kelly; Montani Dominick; Cramer Martin S; Engle Steven D; Jakubowski Joseph A; Heuer Josef G; Grinnell Brian W
Biotechnology Discovery Research, Lilly Corporate Center, Indianapolis, IN 46285, USA.
Clinical and vaccine immunology - CVI (United States) Mar 2006, 13 (3) p426-32, ISSN 1556-6811--Print Journal Code: 101252125
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM

Record type: MEDLINE; Completed
Low levels of protein C (PC) predict outcome as early as 10 h after insult in a rat polymicrobial sepsis model and were associated with suppression of PC mRNA, upstream transcription factor FoxA2, and cofactor hepatocyte nuclear factor 6 (HNF6). Small interfering RNA suppression of FoxA2 in isolated hepatocytes demonstrated regulation of both its cofactor HNF6 and PC. Our data suggest that reduced FoxA2 may be important in the suppression of PC and resulting poor outcome in sepsis.

12/3,AB/9
DIALOG(R)File 155:MEDLINE(R)

19999486 PMID: 16397559
Foxa2, a novel transcriptional regulator of insulin sensitivity.
Puigserver Pere; Rodgers Joseph T
Nature medicine (United States) Jan 2006, 12 (1) p38-9, ISSN 1078-8956--Print Journal Code: 9502015
Publishing Model Print
Document type: News
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

12/3,AB/10
DIALOG(R)File 155:MEDLINE(R)

19698204 PMID: 15567715
Immunohistochemical localization of Foxa1 and Foxa2 in mouse embryos and adult tissues.
Besnard Valerie; Wert Susan E; Hull William M; Whitsett Jeffrey A
Division of Pulmonary Biology, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA.
Gene expression patterns - GEP (Netherlands) Dec 2004, 5 (2) p193-208, ISSN 1567-133X--Print Journal Code: 101167473
Contract/Grant No.: HL53687; HL; NHLBI; HL61646; HL; NHLBI
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Members of the Forkhead box (Fox) transcription factors family Foxa1 (Hnf-3 alpha), Foxa2 (Hnf-3 beta) are known to influence gene expression in endodermally derived tissues including lung, liver, pancreas, stomach, and intestine. In the present study, we have generated highly specific antibodies for Foxa1 and Foxa2 and determined their expression patterns in the developing and adult mouse. Foxa1 and Foxa2 were detected in the nuclei of tissues derived from both foregut and hindgut endoderm (liver, lung, pancreas, stomach, intestine, prostate and bladder). Foxa2 and Foxa1 were also detected in organs deriving from ectodermal (several brain structures and olfactory epithelium) and mesodermal origins (kidney, vagina and uterus, seminal and coagulating glands) during development. Colocalization and distinct sites of expression of Foxa1 and Foxa2 indicate unique as well as overlapping roles of Foxa1 or Foxa2 during morphogenesis and in the function of different adult organs.

12/3,AB/11
DIALOG(R)File 155:MEDLINE(R)

19648922 PMID: 16207754
Tead proteins activate the Foxa2 enhancer in the node in cooperation with a second factor.
Sawada Atsushi; Nishizaki Yuriko; Sato Hiroko; Yada Yukari; Nakayama Rika ; Yamamoto Shinji; Nishioka Noriyuki; Kondoh Hisato; Sasaki Hiroshi
Laboratory for Embryonic Induction, RIKEN Center for Developmental Biology, 2-2-3 Minatojima-minamimachi, Kobe, Hyogo 650-0047, Japan.
Development (Cambridge, England) (England) Nov 2005, 132 (21) p4719-29, ISSN 0950-1991--Print Journal Code: 8701744
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The cell population and the activity of the organizer change during the course of development. We addressed the mechanism of mouse node development via an analysis of the node/notochord enhancer (NE) of Foxa2. We first identified the core element (CE) of the enhancer, which in multimeric form drives gene expression in the node. The CE was activated in Wnt/beta-catenin-treated P19 cells with a time lag, and this activation was dependent on two separate sequence motifs within the CE. These same motifs were also required for enhancer activity in transgenic embryos. We identified the Tead family of transcription factors as binding proteins for the 3' motif. Teads and their co-factor YAP65 activated the CE in P19 cells, and binding of Tead to CE was essential for enhancer activity. Inhibition of Tead activity by repressor-modified Tead compromised NE enhancer activation and notochord development in transgenic mouse embryos. Furthermore, manipulation of Tead activity in zebrafish embryos led to altered expression of foxa2 in the embryonic shield. These results suggest that Tead activates the Foxa2 enhancer core element in the mouse node in cooperation with a second factor that binds to the 5' element, and that a similar mechanism also operates in the zebrafish shield.

12/3,AB/12
DIALOG(R)File 155:MEDLINE(R)

15576619 PMID: 16098831
Foxa2 integrates the transcriptional response of the hepatocyte to fasting.
Zhang Liping; Rubins Nir E; Ahima Rexford S; Greenbaum Linda E; Kaestner Klaus H
Department of Genetics, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.
Cell metabolism (United States) Aug 2005, 2 (2) p141-8, ISSN 1550-4131--Print Journal Code: 101233170
Contract/Grant No.: DK49210; DK; NIDDK; DK56947; DK; NIDDK
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Survival during prolonged food deprivation depends on the activation of hepatic gluconeogenesis. Inappropriate regulation of this process is a hallmark of diabetes and other metabolic diseases. Activation of the genes encoding gluconeogenic enzymes is mediated by hormone-responsive transcription factors such as the cyclic AMP response element binding protein (CREB) and the glucocorticoid receptor (GR). Here we show using cell-type-specific gene ablation that the winged helix transcription factor Foxa2 is required for activation of the hepatic gluconeogenic program during fasting. Specifically, Foxa2 promotes gene activation both by cyclic

AMP, the second messenger for glucagon, and glucocorticoids. Foxa2 mediates these effects by enabling recruitment of CREB and GR to their respective target sites in chromatin. We conclude that Foxa2 is required for execution of the hepatic gluconeogenic program by integrating the transcriptional response of the hepatocyte to hormonal stimulation.

12/3,AB/13
DIALOG(R)File 155:MEDLINE(R)

15561893 PMID: 16055718
Transcriptional networks in the liver: hepatocyte nuclear factor 6 function is largely independent of Foxa2.
Rubins Nir E; Friedman Joshua R; Le Phillip P; Zhang Liping; Brestelli John; Kaestner Klaus H
Department of Genetics, University of Pennsylvania, Philadelphia, 19104, USA.
Molecular and cellular biology (United States) Aug 2005, 25 (16) p7069-77, ISSN 0270-7306--Print Journal Code: 8109087
Contract/Grant No.: DK49210; DK; NIDDK; DK56947; DK; NIDDK
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
A complex network of hepatocyte nuclear transcription factors, including HNF6 and Foxa2, regulates the expression of liver-specific genes. The current model, based on in vitro studies, suggests that HNF6 and Foxa2 interact physically. This interaction is thought to synergistically stimulate Foxa2-dependent transcription through the recruitment of p300/CBP by HNF6 and to inhibit HNF6-mediated transcription due to the interference of Foxa2 with DNA binding by HNF6. To test this model in vivo, we utilized hepatocyte-specific gene ablation to study the binding of HNF6 to its targets in the absence of Foxa2. Chromatin immunoprecipitation using anti-HNF6 antibodies was performed on chromatin isolated from Foxa2(loxP/loxP) Alfp.Cre and control mouse livers, and HNF6 binding to its target, Glut2, was determined by quantitative PCR. In contrast to the current model, we found no significant difference in HNF6 occupancy at the Glut2 promoter between Foxa2-deficient and control livers. In order to evaluate the Foxa2/HNF6 interaction model on a global scale, we performed a location analysis using a microarray with 7,000 mouse promoter fragments. Again, we found no evidence that HNF6 binding to its targets in chromatin is reduced in the presence of Foxa2. We also examined the mRNA levels of HNF6 targets in the liver using a cDNA array and found that their expression was similar in Foxa2-deficient and control mice. Overall, our studies demonstrate that HNF6 binds to and regulates its target promoters in vivo in the presence and absence of Foxa2.

12/3,AB/14
DIALOG(R)File 155:MEDLINE(R)

15532891 PMID: 16003909
Homeobox B3, FoxA1 and FoxA2 interactions in epithelial lung cell differentiation of the multipotent M3E3/C3 cell line.
Yoshimi Tatsuya; Nakamura Nobuatsu; Shimada Sayaka; Iguchi Koichi; Hashimoto Fumiko; Mochitate Katsumi; Takahashi Yuji; Miura Takashi
Laboratory of Environmental Molecular Physiology, School of Life Science, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan. vzz05106@nifty.com
European journal of cell biology (Germany) Jun 2005, 84 (5)

p555-66, ISSN 0171-9335--Print Journal Code: 7906240
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

HOM/C homeobox (Hox) and forkhead box (Fox) factors are reported to be expressed in the foregut endoderm and are subsequently detected in a spatio-temporal pattern during lung development. Some of these factors were reported to influence the expression of lung marker proteins or to modulate lung development. To clarify the molecular mechanisms for generating functional lung cells from progenitor cell populations, we introduced the forkhead box factors, FoxA1 and FoxA2, and the homeobox factor, HoxB3, into the differentiation process in a multipotent hamster lung epithelial M3E3/C3 cell line. Ectopic expression of FoxA2 promoted differentiation to Clara-like cells with up-regulation of the expression of the lung marker proteins, Clara cell-specific 10-kDa protein and surfactant protein-B. In contrast, FoxA1 repressed the differentiation. HoxB3 transfection induced FoxA2 expression transiently at the pre-differentiation stage. The endogenous HoxB3 expression level decreased at later stages of Clara-like cell differentiation, and the attenuation was enhanced by FoxA2 transfection. HoxB3 is a putative upstream regulator that enhances FoxA2 expression at the pre-differentiation stage. In addition, we found that the expression of HoxA4, HoxA5, and HoxC9 increased differentially during Clara-like cell differentiation. These results suggest that HoxB3 may be a putative positive regulator of FoxA2 expression at the pre-differentiation stage, and those interactions of Fox factors and Hox factors could participate in Clara cell differentiation.

12/3,AB/15
DIALOG(R)File 155:MEDLINE(R)

15398384 PMID: 15668254
Compensatory roles of Foxa1 and Foxa2 during lung morphogenesis.
Wan Huajing; Dingle Sharon; Xu Yan; Besnard Valerie; Kaestner Klaus H; Ang Siew-Lan; Wert Susan; Stahlman Mildred T; Whitsett Jeffrey A
Division of Pulmonary Biology, Cincinnati Children's Hospital Medical Center and the University of Cincinnati College of Medicine, Cincinnati, Ohio 45229-3039, USA.
Journal of biological chemistry (United States) Apr 8 2005, 280 (14) p13809-16, ISSN 0021-9258--Print Journal Code: 2985121R
Contract/Grant No.: HL38859; HL; NHLBI; HL56387; HL; NHLBI; HL75770; HL; NHLBI
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Foxa1 and Foxa2 are closely related family members of the Foxa group of transcription factors that are coexpressed in subsets of respiratory epithelial cells throughout lung morphogenesis. Shared patterns of expression, conservation of DNA binding, and transcriptional activation domains indicate that they may serve complementary functions in the regulation of gene expression during lung morphogenesis. Whereas branching morphogenesis of the fetal lung occurs normally in the Foxa2Delta/Delta and Foxa1-/- mice, deletion of both Foxa1 and Foxa2 (in Foxa2Delta/Delta, Foxa1-/- mice) inhibited cell proliferation, epithelial cell differentiation, and branching. Dilation of terminal lung tubules and decreased branching were observed as early as embryonic day 12.5. Foxa1 and Foxa2 regulated Shh (sonic hedgehog) and Shh-dependent genes in the respiratory epithelial cells that influenced the expression of genes in the

pulmonary mesenchyme that are required for branching morphogenesis. Epithelial cell differentiation, as indicated by lack of expression of surfactant protein B, surfactant protein C, the Clara cell secretory protein, and Foxj1, was inhibited. Foxa family members regulate signaling and transcriptional programs required for morphogenesis and cell differentiation during formation of the lung.

12/3,AB/16
DIALOG(R)File 155:MEDLINE(R)

15311862 PMID: 15680365
Foxa2 is required for the differentiation of pancreatic alpha-cells.
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Department of Genetics and Penn Diabetes Center, University of Pennsylvania School of Medicine, 415 Curie Boulevard, CRB 560 Philadelphia, PA 19104, USA.
Developmental biology (United States) Feb 15 2005, 278 (2) p484-95, ISSN 0012-1606--Print Journal Code: 0372762
Contract/Grant No.: DK49210; DK; NIDDK; DK55342; DK; NIDDK; DK61226; DK; NIDDK
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The differentiation of insulin-producing beta-cells has been investigated in great detail; however, little is known about the factors that delineate the second-most abundant endocrine lineage, the glucagon-producing alpha-cell. Here we utilize a novel YAC-based Foxa3Cre transgene to delete the winged helix transcription factor Foxa2 (formerly HNF-3beta) in the pancreatic primordium during midgestation. The resulting Foxa2(loxP/loxP); Foxa3Cre mice are severely hypoglycemic and die within the first week of life. Mutant mice are hypoglucagonemic secondary to a 90% reduction of glucagon expression. While the number of mature glucagon-positive alpha-cells is dramatically reduced, specification of alpha-cell progenitors is not affected by Foxa2 deficiency. By marker gene analysis, we show that the expression of the alpha-cell transcription factors Arx, Pax6, and Brn4 does not require Foxa2 in the transcriptional hierarchy governing alpha-cell differentiation.

12/3,AB/17
DIALOG(R)File 155:MEDLINE(R)

15310017 PMID: 15677724
Monorail/Foxa2 regulates floorplate differentiation and specification of oligodendrocytes, serotonergic raphe neurones and cranial motoneurones.
Norton Will H; Mangoli Maryam; Lele Zsolt; Pogoda Hans-Martin; Diamond Brianne; Mercurio Sara; Russell Claire; Teraoka Hiroki; Stickney Heather L; Rauch Gerd-Jorg; Heisenberg Carl-Philipp; Houart Corinne; Schilling Thomas F; Frohnhoefer Hans-Georg; Rastegar Sepand; Neumann Carl J; Gardiner R Mark ; Strahle Uwe; Geisler Robert; Rees Michelle; Talbot William S; Wilson Stephen W
Department of Anatomy and Developmental Biology, UCL, Gower Street, London WC1E 6BT, UK.
Development (Cambridge, England) (England) Feb 2005, 132 (4) p645-58, ISSN 0950-1991--Print Journal Code: 8701744

10/614481 09/07/2006

Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

In this study, we elucidate the roles of the winged-helix transcription factor Foxa2 in ventral CNS development in zebrafish. Through cloning of monorail (mol), which we find encodes the transcription factor Foxa2, and phenotypic analysis of mol-/- embryos, we show that floorplate is induced in the absence of Foxa2 function but fails to further differentiate. In mol-/- mutants, expression of Foxa and Hh family genes is not maintained in floorplate cells and lateral expansion of the floorplate fails to occur. Our results suggest that this is due to defects both in the regulation of Hh activity in medial floorplate cells as well as cell-autonomous requirements for Foxa2 in the prospective laterally positioned floorplate cells themselves. Foxa2 is also required for induction and/or patterning of several distinct cell types in the ventral CNS. Serotonergic neurones of the raphenucleus and the trochlear motor nucleus are absent in mol-/- embryos, and oculomotor and facial motoneurones ectopically occupy ventral CNS midline positions in the midbrain and hindbrain. There is also a severe reduction of prospective oligodendrocytes in the midbrain and hindbrain. Finally, in the absence of Foxa2, at least two likely Hh pathway target genes are ectopically expressed in more dorsal regions of the midbrain and hindbrain ventricular neuroepithelium, raising the possibility that Foxa2 activity may normally be required to limit the range of action of secreted Hh proteins.

12/3,AB/18
DIALOG(R)File 155:MEDLINE(R)

15224409 PMID: 15616563

Foxa2 regulates lipid metabolism and ketogenesis in the liver during fasting and in diabetes.

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Nature (England) Dec 23 2004, 432 (7020) p1027-32, ISSN 1476-4687--Electronic Journal Code: 0410462

Publishing Model Print; Comment in Nature. 2004 Dec 23;432(7020) 958-9; Comment in PMID 15616540

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

The regulation of fat and glucose metabolism in the liver is controlled primarily by insulin and glucagon. Changes in the circulating concentrations of these hormones signal fed or starvation states and elicit counter-regulatory responses that maintain normoglycaemia. Here we show that in normal mice, plasma insulin inhibits the forkhead transcription factor Foxa2 by nuclear exclusion and that in the fasted (low insulin) state Foxa2 activates transcriptional programmes of lipid metabolism and ketogenesis. In insulin-resistant or hyperinsulinaemic mice, Foxa2 is inactive and permanently located in the cytoplasm of hepatocytes. In these mice, adenoviral expression of Foxa2T156A, a nuclear, constitutively active Foxa2 that cannot be inhibited by insulin, decreases hepatic triglyceride content, increases hepatic insulin sensitivity, reduces glucose production, normalizes plasma glucose and significantly lowers plasma insulin. These changes are associated with increased expression of genes encoding enzymes of fatty acid oxidation, ketogenesis and glycolysis. Chronic hyperinsulinaemia in insulin-resistant syndromes results in the cytoplasmic

localization and inactivation of Foxa2, thereby promoting lipid accumulation and insulin resistance in the liver. Pharmacological intervention to inhibit phosphorylation of Foxa2 may be an effective treatment for type 2 diabetes.

12/3,AB/19
DIALOG(R)File 155:MEDLINE(R)

15184409 PMID: 15385550
Regulation of the cell-specific calcitonin/calcitonin gene-related peptide enhancer by USF and the Foxa2 forkhead protein.
Viney Tim J; Schmidt Thomas W; Gierasch William; Sattar A Wahed; Yaggie Ryan E; Kuburas Adisa; Quinn John P; Coulson Judy M; Russo Andrew F
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Journal of biological chemistry (United States) Nov 26 2004, 279 (48) p49948-55, ISSN 0021-9258--Print Journal Code: 2985121R
Contract/Grant No.: HD 25969; HD; NICHD
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
An 18-bp enhancer controls cell-specific expression of the calcitonin/calcitonin gene-related peptide gene. The enhancer is bound by a heterodimer of the bHLH-Zip protein USF-1 and -2 and a cell-specific factor from thyroid C cell lines. In this report we have identified the cell-specific factor as the forkhead protein Foxa2 (previously HNF-3beta). Binding of Foxa2 to the 18-bp enhancer was demonstrated using electrophoretic mobility shift assays. The cell-specific DNA-protein complex was selectively competed by a series of Foxa2 DNA binding sites, and the addition of Foxa2 antiserum supershifted the complex. Likewise, a complex similar to that seen with extracts from thyroid C cell lines was generated using an extract from heterologous cells expressing recombinant Foxa2. Interestingly, overexpression of Foxa2 activated the 18-bp enhancer in heterologous cells but only in the presence of the adjacent helix-loop-helix motif. Likewise, coexpression of USF proteins with Foxa2 yielded greater activation than by Foxa2 alone. Unexpectedly, Foxa2 overexpression repressed activity in the CA77 thyroid C cell line, suggesting that Foxa2 may interact with additional cofactors. The stimulatory role of Foxa2 at the calcitonin/calcitonin gene-related peptide gene enhancer was confirmed by short interfering RNA-mediated knockdown of Foxa2. As seen with Foxa2 overexpression, the effect of Foxa2 knockdown also required the adjacent helix-loop-helix motif. These results provide the first evidence for combinatorial control of gene expression by bHLH-Zip and forkhead proteins.

12/3,AB/20
DIALOG(R)File 155:MEDLINE(R)

15111744 PMID: 15452354
Foxa2 is required for transition to air breathing at birth.
Wan Huajing; Xu Yan; Ikegami Machiko; Stahlman Mildred T; Kaestner Klaus H; Ang Siew-Lan; Whitsett Jeffrey A
Division of Pulmonary Biology, Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, 3333 Burnet Avenue, Cincinnati, OH 45229-3039, USA.
Proceedings of the National Academy of Sciences of the United States of America (United States) Oct 5 2004, 101 (40) p14449-54, ISSN

10/614481 09/07/2006

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Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Toward the end of gestation in mammals, the fetal lung undergoes a process of differentiation that is required for transition to air breathing at birth. Respiratory epithelial cells synthesize the surfactant proteins and lipids that together form the pulmonary surfactant complex necessary for lung function. Failure of this process causes respiratory distress syndrome, a leading cause of perinatal death and morbidity in newborn infants. Here we demonstrate that expression of the forkhead gene Foxa2 in respiratory epithelial cells of the peripheral lung controls pulmonary maturation at birth. Newborn mice lacking Foxa2 expression in the lung develop severe pulmonary disease on the first day of life, with all of the morphological, molecular, and biochemical features of respiratory distress syndrome in preterm infants, including atelectasis, hyaline membranes, and the lack of pulmonary surfactant lipids and proteins. RNA microarray analysis at embryonic day 18.5 demonstrated that Foxa2-regulated expression of a group of genes mediating surfactant protein and lipid synthesis, host defense, and antioxidant production. Foxa2 regulates a complex pulmonary program of epithelial cell maturation required for transition to air breathing at birth.

12/3,AB/21
DIALOG(R)File 155:MEDLINE(R)

15032194 PMID: 15314688
Foxa2 regulates multiple pathways of insulin secretion.
Lantz Kristen A; Vatamaniuk Marko Z; Brestelli John E; Friedman Joshua R; Matschinsky Franz M; Kaestner Klaus H
Department of Genetics, Children's Hospital of Philadelphia, Philadelphia, PA, USA.
Journal of clinical investigation (United States) Aug 2004, 114 (4) p512-20, ISSN 0021-9738--Print Journal Code: 7802877
Contract/Grant No.: R01 DK 55342; DK; NIDDK; U01 DK 56947; DK; NIDDK
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

The regulation of insulin secretion by pancreatic beta cells is perturbed in several diseases, including adult-onset (type 2) diabetes and persistent hyperinsulinemic hypoglycemia of infancy (PHHI). The first mouse model for PHHI has a conditional deletion of the gene encoding the winged-helix transcription factor Foxa2 (Forkhead box a2, formerly Hepatocyte nuclear factor 3beta) in pancreatic beta cells. Using isolated islets, we found that Foxa2 deficiency resulted in excessive insulin release in response to amino acids and complete loss of glucose-stimulated insulin secretion. Most PHHI cases are associated with mutations in SUR1 (Sulfonylurea receptor 1) or KIR6.2 (Inward rectifier K(+) channel member 6.2), which encode the subunits of the ATP-sensitive K(+) channel, and RNA in situ hybridization of mutant mouse islets revealed that expression of both genes is Foxa2 dependent. We utilized expression profiling to identify additional targets of Foxa2. Strikingly, one of these genes, Hadhsc, encodes short-chain L-3-hydroxyacyl-coenzyme A dehydrogenase, deficiency of which has been shown to cause PHHI in humans. Hadhsc is a direct target of Foxa2, as demonstrated by cotransfection as well as in vivo chromatin immunoprecipitation experiments using isolated islets. Thus, we have established Foxa2 as an essential activator of genes that function in

multiple pathways governing insulin secretion.

12/3,AB/22
DIALOG(R)File 155:MEDLINE(R)

14734536 PMID: 14757645
Foxa2 regulates alveolarization and goblet cell hyperplasia.
Wan Huajing; Kaestner Klaus H; Ang Siew-Lan; Ikegami Machiko; Finkelman Fred D; Stahlman Mildred T; Fulkerson Patricia C; Rothenberg Marc E; Whitsett Jeffrey A
Division of Pulmonary Biology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229-3039, USA.
Development (Cambridge, England) (England) Feb 2004, 131 (4) p953-64, ISSN 0950-1991--Print Journal Code: 8701744
Contract/Grant No.: HL56387; HL; NHLBI
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The airways are lined by several distinct epithelial cells that play unique roles in pulmonary homeostasis; however, the mechanisms controlling their differentiation in health and disease are poorly understood. The winged helix transcription factor, FOXA2, is expressed in the foregut endoderm and in subsets of respiratory epithelial cells in the fetal and adult lung. Because targeted mutagenesis of the Foxa2 gene in mice is lethal before formation of the lung, its potential role in lung morphogenesis and homeostasis has not been determined. We selectively deleted Foxa2 in respiratory epithelial cells in the developing mouse lung. Airspace enlargement, goblet cell hyperplasia, increased mucin and neutrophilic infiltration were observed in lungs of the Foxa2-deleted mice. Experimental goblet cell hyperplasia caused by ovalbumin sensitization, interleukin 4 (IL4), IL13 and targeted deletion of the gene encoding surfactant protein C (SP-C), was associated with either absent or decreased expression of Foxa2 in airway epithelial cells. Analysis of lung tissue from patients with a variety of pulmonary diseases revealed a strong inverse correlation between FOXA2 and goblet cell hyperplasia. FOXA2 is required for alveolarization and regulates airway epithelial cell differentiation in the postnatal lung.

12/3,AB/23
DIALOG(R)File 155:MEDLINE(R)

14691691 PMID: 14697355
Inhibition of mesodermal fate by Xenopus HNF3beta/FoxA2.
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Department of Pharmacology and Biological Chemistry, Mount Sinai School of Medicine, New York, NY 10029, USA.
Developmental biology (United States) Jan 1 2004, 265 (1) p90-104, ISSN 0012-1606--Print Journal Code: 0372762
Contract/Grant No.: GM-62754; GM; NIGMS; R01-GM61671; GM; NIGMS
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The winged-helix transcription factor HNF3beta/FoxA2 is expressed in embryonic organizing centers of the gastrulating mouse, frog, fish, and chick. In the mouse, HNF3beta is required for the formation of the

mammalian node and notochord, and can induce ectopic floor plate formation when misexpressed in the developing neural tube; HNF3beta expression in the extraembryonic endoderm is also necessary for the proper morphogenesis of the mammalian primitive streak. In the frog Xenopus laevis, several lines of evidence suggest that the related winged-helix factor Pintallavis functions as the ortholog of mammalian HNF3beta in both axial mesoderm and neurectoderm; the role of Xenopus HNF3beta itself, however, has not been clearly defined, and is the subject of this study. HNF3beta is widely expressed in the vegetal pole but, as previously suggested, is excluded from the gastrula-stage mesoderm. We find that expression of an HNF3beta-Engrailed repressor fusion protein induces ectopic axes and inhibits head formation in Xenopus embryos, while ectopic HNF3beta inhibits mesoderm and anterior endoderm formation in explant assays and in vivo. Our studies suggest that HNF3beta target genes function to limit the extent of mesoderm formation in the Xenopus gastrula, and point to related roles for Xenopus HNF3beta and the extraembryonic component of mammalian HNF3beta during vertebrate gastrulation.